Small Animal CRITICAL CARE MEDICINE

Deborah Silverstein

Kate Hopper

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Front Matter

Dedication

“One looks back with appreciation to the brilliant teachers, but with gratitude to those who touched our human feeling. Curriculum is necessary raw material, but warmth is the vital element for the growing plant and for the soul of the child.”

–Carl Jung

With special thanks to: –My husband, Stefan, and sons, Maxwell and Henry, for their infinite warmth, love, and support,–My grandma Leona, mom (Judy), dad (Paul and wife Amalia), brothers (Steve and Bruce), and sister (Andrea) for always believing in me,–Dr. Lesley King for her guidance,–And my extended family and friends who helped me smile despite it all!

–Deborah Silverstein

To my parents Max and Joyce, my sister Jane, and my brother Bill for their endless love and support, and to my friends who have made it all worthwhile.

–Kate Hopper

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Preface

Veterinary practitioners are often faced with the need to care for critically ill and traumatized patients on a moment's notice. After-hours emergency and critical care facilities are in increasing demand as pet owners are ever-more likely and willing to take their pets to such facilities when life-threatening conditions arise. As a consequence of this demand and client expectations, veterinarians are increasingly aware that they must provide state-of-the-art critical care therapy and monitoring for their patients and that their preparedness for such situations is imperative.

WHY IS THIS BOOK IMPORTANT?

Veterinary critical care medicine is still a relatively new but rapidly emerging specialty that is focused on providing life-sustaining therapy and support systems for desperately ill and traumatized patients who would not survive without them. Critical care medicine encompasses not only the period immediately following hospital presentation but the entire course of acute medical crisis and high risk. It incorporates advanced technology, intensive patient monitoring, and cutting-edge medical concepts. It requires a strong fundamental knowledge of all body systems and a basic understanding of the pathophysiology of disease states—an amount of information that is often daunting and difficult to master.

As anyone teaching or practicing in the field of veterinary critical care knows, there is a deficit of comprehensive texts that provide a practical and action-oriented review of all relevant topics in critical care. Although there are several available texts labeled as “emergency and critical care” resources, they are all heavily weighted toward emergency medicine and fail to adequately address many topics vital to the management of critical care patients. This textbook is the first of its kind devoted to the practice and challenges of critical care medicine as a specialty in its own right. We intend for it to be an essential, state-of-the-art resource for anyone working with critical patients in general practice clinics, specialty veterinary practices, and university teaching hospitals. It emphasizes interventional therapy in the critically ill or traumatized patient, while addressing important considerations regarding underlying clinical findings, pathophysiology, clinical course and prognosis. The scope of topics is broad and clinically oriented, helping the practitioner provide the highest standard of care for their critically ill and injured patients.

ORGANIZATION

This book is the compilation of work from many veterinary specialists, all of whom have written on critical care topics in their areas of expertise. It brings many facets of critical care together into a single text source, with topics ranging from the most frequently encountered problems in the intensive care unit to a detailed pharmacology section and advanced critical care procedural and monitoring techniques. The remarkable team of over 150 international experts who have contributed to this text offers in-depth, authoritative guidance on clinical problems from a multitude of perspectives. They provide the most up-to-date information on common problems facing the practitioner and the more challenging aspects of critical care medicine. The focus has been on creating the best organized and most rapidly accessible reference tool for the entire critical care team under some of the most demanding and emotional clinical circumstances.

With 20 major sections and 217 *chapters and appendixes, Small Animal Critical Care Medicine* provides an in-depth resource for the diagnostic, therapeutic, procedural, and management issues pertinent to the critically ill patient. Its user-friendly design makes it an approachable resource while its in-depth content provides essential and often difficult to find information. The book is composed of short, concise chapters and is organized into logical sections, beginning with assessment and triage and covering management approaches for frequently encountered problems seen in patients presenting with critical care issues. The largest part of the book contains sections grouped by organ system, covering common and uncommon diseases, syndromes, and disturbances of homeostasis seen in small animal critical patients. Acute derangements of the respiratory, circulatory, nervous, gastrointestinal, endocrine, renal, and reproductive systems, as well as metabolic and hematologic disorders, are covered. Other sections cover traumatic injuries, perioperative complications, intoxications, inflammatory and infectious diseases, and other miscellaneous disorders not readily classified by organ system or discipline. Special sections featuring clinical procedures, monitoring, anesthesia and pain management, and critical care pharmacology are also included.

DISTINCTIVE FEATURES

This book provides key, in-depth information that covers all aspects of veterinary critical care medicine. It is not only organized with an easy-to-use format for referencing all aspects of critical care medicine, but also contains numerous figures, color plates, and tables for rapidly visualizing the concepts and information presented within the chapters. Chapters provide concise information regarding etiology, differential diagnoses, clinical manifestations, laboratory findings, diagnostic methods, and therapeutic approaches. The key points boxes at the beginning of each chapter enable the reader to rapidly see an overview of the topic, and extensive cross referencing within the chapters allows for further reading of specific topics mentioned within. For further reference or an in-depth review of specific aspects of a particular topic, annotated suggested readings are included at the end of each chapter. Readers wishing more details on pathophysiologic mechanisms or pharmacokinetics and clinical studies are referred to a more extensive list of references in the Companion CD. The inside cover and the appendixes at the end of the text provide valuable information regarding frequently used conversions, key calculations, diagnostic test reference ranges, and one of the most comprehensive lists of constant rate infusion drug doses available.

Critical care medicine poses a unique set of challenges and rewards, and we hope that this book will fill the gap that exists between basic medical and surgical references and the available emergency-oriented manuals. We also hope that this book will enable veterinarians, who have committed themselves to the knowledgeable and skillful care of their patients, to better deliver on that solemn promise and enhance both quality of life for pets and the ongoing relationship with those who love them.

Acknowledgments

The editors are most appreciative to all of the Elsevier staff, especially Tony Winkel, Maureen Slaten, and Beth Hayes. Without the support and dedication of this talented group of individuals, this text would not have been possible.

1 Chapter 1 Physical Examination

Timothy B. Hackett, DVM, MS, DACVECC

1.1 KEY POINTS

- Hands-on assessment of critically ill patients is essential to detect life-threatening changes in their condition.
- Clinicians should use their eyes, ears, hands, and nose to evaluate the critically ill patient before jumping to blood tests, electrodiagnostic techniques, or imaging.
- Physiologic variables related to oxygen delivery take precedence in evaluating the critically ill patient.
- Clinicians and other personnel should note and record both subjective and objective physical examination parameters as often as necessary, taking into consideration the patient's current problems and anticipated complications.

1.2 INTRODUCTION

Physical examination, or more correctly, serial physical examination, is the core of critical care medicine. Sometimes it seems that all intensivists do is monitor, record, and interpret readily available physiologic variables. Although this may be true, it is important to remember why. The goal is to detect problems with organ function before organ dysfunction becomes organ failure.

Technology helps to identify life-threatening problems. Arterial blood gas machines, oscillometric blood pressure monitors, pulse oximeters, ultrasound machines, and portable coagulation analyzers are just a few of the technologic advances that have found their way into 24-hour emergency and critical care veterinary practices. Their appropriate use has improved our ability to provide the best care to our patients. However, with reliance on technology, clinicians may have forgotten some of the “art” of the physical examination. To date there is no readily available technology that can measure adequacy of perfusion or degree of hydration. Although measurement of parameters such as blood pressure provides vital information, it can be interpreted only in light of the physical examination. When a clinician reaches for an ultrasonography probe or electrocardiograph (ECG) before touching the patient with hands and stethoscope, something has been lost.

The physical examination of the critically ill patient is approached much in the same way as for the emergency patient. With focus on the efficacy of oxygen delivery, the first priority is assessing the respiratory and cardiac systems. The ABCs (airway, breathing, and circulation) of resuscitation provide a simple systematic approach to the primary survey.

1.3 AIRWAY AND BREATHING

Patients adapt respirations to minimize the work of breathing. Animals with upper airway obstruction, dynamic airway collapse, bronchitis, or other obstructions to airflow will breathe slowly and deeply. With upper airway and extrathoracic obstructions, the effort will be on inspiration. With obstruction or collapse of the intrathoracic small airways, the effort will be on expiration. By decreasing the force of respiration, this so-called *obstructive breathing pattern* will favor maximal flow through narrowed airways with minimal energy expenditure. The effect of respiratory rate and depth on obstructive breathing can be experienced by trying to breathe through a straw.

Animals with pleural space disease, atelectasis, or pulmonary fibrosis will adopt what is known as a *restrictive breathing pattern*. By minimizing the change in volume while increasing the respiratory rate, they can maintain alveolar minute ventilation despite decreased pulmonary compliance (see Chapter 9, Tachypnea and Hypoxemia).

1.4 CIRCULATION

Alveolar oxygenation is the first essential step in providing adequate oxygen delivery to the tissues. A normal cardiovascular system is then necessary to carry the blood to the lungs for oxygen loading and back to the body. Physical assessment of the circulatory system relies on palpation and observation of venous distention, palpation of the arterial pulse (for synchrony, quality, and heart rate), evaluation of mucous membrane color and capillary refill, and auscultation of the heart and lungs. Inadequate global perfusion is considered an indicator of circulatory shock and is a clinical diagnosis made from physical examination alone.

1.4.1 Heart Rate

A normal heart rate indicates that at least one component of cardiac output is normal. We expect a heart rate of 70 to 120 beats/min in small dogs, 60 to 120 beats/min in large dogs, and 120 to 200 beats/min in cats.

Bradycardia results in decreased cardiac output and subsequent poor perfusion; cats often develop bradycardia (<120 beats/min) in shock, and this can be associated with imminent cardiac arrest. Bradycardia is an unusual finding in a critically ill patient and can result from electrolyte imbalances (hyperkalemia), neurologic disease (increased intracranial pressure), conduction disturbances (atrioventricular block, sick sinus syndrome), or overdose of analgesic or anesthetic drugs. An ECG is indicated for full assessment of bradycardia.

Tachycardia (dogs >180 beats/min, cats >220 beats/min) is the body's response to decreased blood volume, pain,
anxiety, and hypoxemia. Increasing heart rate will temporarily increase cardiac output and oxygen delivery. 2
However, there is some limitation to this response. When the heart rate becomes too fast, diastolic filling is 3
compromised and stroke volume suffers. Sinus tachycardia often results from circulatory shock or pain;
tachycardia that is irregular or associated with pulse deficits usually indicates an arrhythmia, and an ECG is
indicated.

1.4.2 Mucous Membrane Color

Evaluation of mucous membrane color is subjective but can give an experienced clinician a great deal of important information. Pale or white mucous membranes are indicative of anemia or vasoconstrictive shock. Red mucous membranes suggest vasodilation as seen in systemic inflammatory states and hyperthermia. Cyanotic gums indicate a normal packed cell volume (cyanosis will not be clinically evident without adequate hemoglobin) but severe hypoxemia. A yellow hue indicates increased serum bilirubin (from hepatic disease or hemolysis), and a brown color of the gums can be seen with methemoglobinemia. During examination of the gums, petechiation or bleeding should be noted. Thrombocytopenia is an early finding in disseminated intravascular coagulation. Petechiae and bruising are clinical signs of platelet deficiency or dysfunction.

1.4.3 Capillary Refill Time

Evaluation of capillary refill time (CRT) is also subject to interpretation. You may even notice a normal CRT in a recently deceased patient. However, used in conjunction with pulse quality, respiratory effort, heart rate, and gum color, the CRT can help assess a patient's blood volume and peripheral perfusion, and give an insight into causes of a patient's shock. Normal CRT is 1 to 2 seconds. This is consistent with a normal blood volume and perfusion. A CRT longer than 2 seconds is a subjective sign of poor perfusion or peripheral vasoconstriction. Peripheral vasoconstriction is an appropriate response to low circulating blood volume and reduced oxygen delivery to vital tissues. Patients with hypovolemic and cardiogenic shock should be expected to have peripheral vasoconstriction. Peripheral vasoconstriction is also commonly associated with cool extremities, assessed by feeling the distal limbs. A CRT less than 1 second is indicative of a hyperdynamic state and vasodilation (as are bright red mucous membranes). Hyperdynamic states can be associated with systemic inflammation, heat stroke, distributive shock, and hyperthermia.

Venous distention can be a sign of volume overload or right-sided congestive heart failure. Palpation of the jugular vein may demonstrate distention, although it may be easier to appreciate by clipping a small patch of hair over the lateral saphenous vein. With the patient in lateral recumbency, if the lateral saphenous vein in the upper limb appears distended (as if the vessel is being held off), slowly raise the rear leg above the level of the heart. If the vein remains distended, the patient likely has an elevated central venous pressure, and volume overload or diseases causing right-sided congestive heart failure (dilated cardiomyopathy, tricuspid insufficiency, pericardial effusion) should be considered. A patient with pale mucous membranes from vasoconstriction in response to hypovolemia would not be expected to have venous distention. In comparison, cardiogenic shock is more likely to cause pale mucous membranes and increased venous distention.

1.4.4 Pulse Quality

The pulse should be palpated while listening to the heart or palpating the apex. A strong pulse that is synchronous with each heartbeat is normal and consistent with adequate blood volume and cardiac output. Digital palpation of pulse quality as assessed by digital palpation is largely a reflection of pulse pressure. Pulse pressure equals the difference between the systolic and diastolic arterial blood pressures. Hence a normal pulse pressure may be present despite abnormal systolic and diastolic pressures. For this reason digital palpation of pulse quality is a very poor indicator of arterial blood pressure. Both the femoral and dorsal pedal pulses should be palpated. It is said that a palpable dorsal pedal arterial pulse indicates a systolic blood pressure of at least 80 mm Hg, although experienced clinicians will find they are able to feel these pulses in hypotensive patients. An irregular pulse or one that is asynchronous with cardiac auscultation is a sign of a significant cardiac arrhythmia. An ECG can confirm the arrhythmia and help determine the best treatment.

Bounding pulses indicate either a hyperdynamic state (as discussed with rapid CRTs) or some form of diastolic run-off (such as a patent ductus arteriosus or aortic insufficiency). Close attention to cardiac auscultation for holosystolic or diastolic murmurs can help refine the list of possible causes. Remember, a pulse indicates only the difference in systolic and diastolic arterial blood pressure and does not give accurate information on systemic mean arterial blood pressure.

Weak pulses are a common finding in the critically ill and can be due to decreased cardiac output (either low stroke volume or decreased contractility), peripheral vasoconstriction, or decreased pulse pressure. The response to intravenous fluid therapy will help distinguish among the causes of shock.

1.5 AUSCULTATION

Cardiac and pulmonary auscultation is an essential part of the physical examination. Clinicians and critical care nurses should perform serial auscultation throughout a patient's hospital stay. Nursing staff and clinicians should auscultate the heart and pulmonary sounds at least twice during a shift, once at the beginning and once before they leave. Subtle changes in respiratory noise can signal early problems with fluid overload or aspiration pneumonia.

The respiratory system should be evaluated from the nasal sinuses, the larynx and trachea, down to all the lung fields. Stertor and wheezes in the upper airways and quiet crackles in the lungs may be an early sign of fluid overload. Inspiratory stridor can be heard with laryngeal paralysis, and expiratory wheezes indicate small airway collapse and bronchitis. Crackles across the lung fields can be heard with pneumonia or pulmonary edema. Aspiration pneumonia often affects the cranioventral lungs, and pulmonary edema may begin in the perihilar fields near the base of the heart. Decreased lung sounds may be heard with consolidation of the lungs, pneumothorax, and pleural effusion. With pleural effusion, a fluid line may be detected by ausculting the standing patient's chest. Changes in lung sounds may be an indication for thoracic radiography. Critically ill patients should have their oxygenating ability assessed frequently with pulse oximetry or arterial blood gas measurement, or both. Any change in respiratory character or sounds should prompt immediate reevaluation of oxygenation status. 3

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Cardiac auscultation should be repeated at least once daily. As mentioned with pulse quality, the pulse should be palpated while listening to the heart. New murmurs or asynchronous pulses should be noted and investigated. Cardiac arrhythmias in the critically ill are an early sign of cardiac dysfunction. As with failure of any organ system, these abnormalities should be investigated and underlying metabolic or oxygen delivery problems corrected.

1.6 LEVEL OF CONSCIOUSNESS

The patient's level of consciousness and response to surroundings should be assessed frequently. If the patient appears normal, alert, and responsive we can be happy with overall neurologic and metabolic status. Patients that are obtunded (“depressed” indicates a feeling and is not applicable to our patients) or less responsive to visual and tactile stimuli may be suffering from a variety of complications and illnesses. Stupor (can be aroused only with painful stimuli) is a sign of severe neurologic or metabolic derangements. Coma (cannot be aroused with any stimuli) and seizures are signs of abnormal cerebral electrical activity from primary neurologic disease or secondary to metabolic derangements such as hepatic encephalopathy. One of the most concerning issues in the critically ill patient is any decrease in the gag reflex. This may be a result of a general decrease in the level of consciousness or primary neurologic deficit. A decrease in the gag reflex places the animal at high risk of aspiration, a potentially fatal complication. Oral intake should be withheld in animals with a compromised gag reflex, and if the gag reflex is absent, immediate endotracheal intubation to protect the airway is indicated.

1.7 TEMPERATURE

Body temperature should be monitored frequently, if not continuously, in the critically ill patient. Hyperthermia should be differentiated from true fever. Hospitalized animals may develop hyperthermia from cage heat or heating pads. True fever should be investigated quickly, because systemic inflammation and infectious complications are common problems in the critically ill.

Many critically ill animals have difficulty maintaining their body temperature and require external heat supplementation. Heat may be supplied by placing warm water-filled gloves or bottles in towels next to the animal. Heating pads should be used with caution; use a low temperature setting and insulate the animal with a blanket or fleece pad. Heat lamps should be used from a distance of more than 30 inches to prevent burns. Circulating hot water blankets can be used to increase body temperature. Circulating hot air systems (Bair Hugger) are another excellent source for active rewarming. Electric cage dryers or hand-held blow dryers are useful if the animal is already wet. A warming waterbed can be made by placing a thick plastic bag over an appropriate-size container filled with warm water. A towel is placed under the animal to prevent its nails from perforating the plastic and burning the patient, and blankets are placed on top of the animal to prevent heat from escaping. Intravenous fluids warmed to body temperature usually help increase body temperature. To prevent overwarming, body temperature should be monitored at regular intervals and warming measures discontinued when the body temperature reaches 100° F. Animals should be monitored carefully to prevent iatrogenic hyperthermia and burns.

1.8 HYDRATION

Although many issues related to assessing blood volume and the adequate circulation have been addressed, it is important to gauge fluid balance of critically ill patients. Hydration status is a measure of interstitial fluid content; in comparison, perfusion parameters (mucous membrane color, CRT, heart rate) are a measure of intravascular volume. It is important to assess both of these parameters separately and alter the fluid plan accordingly. Daily body weight is the most objective way to monitor hydration. Day-to-day changes in body weight reflect fluid balance. A dehydrated patient should gain weight as fluid spaces are rehydrated, and overhydration will be associated with progressive increases in weight. Hydration is assessed clinically by evaluation of skin turgor (skin elasticity). With dehydration skin turgor decreases and skin tenting becomes prolonged. With overhydration skin turgor increases and the subcutaneous tissues gain a “jelly-like” consistency. A serous nasal discharge, peripheral edema, and chemosis are also signs of overhydration. Peripheral edema can occur with overhydration; it can also indicate vasculitis or decreased oncotic pressure (hypoproteinemia). Skin turgor in cachectic and obese animals can be very difficult to assess.

Clinicians should also be wary of third space fluid accumulation. Third-space fluid loss is fluid collection within tissues or a body cavity that does not contribute to circulation. Pleural and abdominal effusions could lead to increases in body weight or maintenance of body weight while the patient becomes clinically hypovolemic. Daily (more often when appropriate) calculation of fluid balance is essential in critically ill animals. This requires accurate measurement of all fluid intake and output including food and water intake, urine, vomit, and feces. Significant discrepancies in the volume of intake versus output require complete reevaluation of the patient and alteration of the fluid plan accordingly.

1.9 GASTROINTESTINAL SYSTEM

The gastrointestinal (GI) tract may be difficult to evaluate but not impossible. It must be remembered that GI problems are seen often with circulatory shock and critical illness. The frequency, character, and volume of GI losses should be monitored. If fresh or digested blood is observed, GI protectants and antibiotics may be indicated. A rectal examination and close inspection of rectal thermometers are good ways to evaluate stool quality. Vomiting should be distinguished from regurgitation, and any retching or vomiting dog should be monitored for gastric dilatation-volvulus.

1.10 NURSING CARE

Recumbent patients require attentive nursing care to prevent complications. Pressure points over bony protuberances should be massaged regularly and padded heavily to prevent decubitus ulcers. The best treatment for decubitus ulcers is prevention. Once formed, they should be debrided and kept as clean, dry, and pressure-free as possible. These 4
ulcers may be a significant source of infectionand may warrant antimicrobial therapy. Patients should be turned 5
frequently (every 2 to 4 hours) to help prevent lung consolidation and pneumonia. The cage should be set up so that urine and diarrhea drain away from the animal. Urine and fecal scald can cause significant problems and should be prevented. Water-based ointment may be applied to the skin around clean genital and perineal areas for protection from scald. Bladder size should be monitored frequently, especially in animals with spinal disease, and the bladder

expressed regularly if necessary. Animals should be observed for fecal impaction, and enemas or manual evacuation performed as necessary.

Patients should be kept clean, dry, warm, and as comfortable and pain free as possible. Bandages, dressings, and drains should be monitored closely for local swelling or other complications and changed when soiled. Eye ointment should be applied regularly to prevent corneal ulcers in patients that fail to blink adequately. Appropriate pain control should always be provided. Any large breed painful, anxious dog that is in pain should be monitored for gastric dilatation-volvulus. Nutritional needs should be aggressively addressed. Postoperative patients should receive at least 30 kcal/kg q24h. Frequent, hands-on contact with the patient is invaluable in high-quality clinical assessment and monitoring. Owner visits often improve the attitude of the patient and provide insights on their behavior. Compassionate care cannot be overemphasized as one of the important factors for recovery.

1.11 SUGGESTED FURTHER READING*

J Aldrich: Global assessment of the emergency patient. *Vet Clin North Am Small Anim Pract*. **35**, 2005, 281, *An excellent, in-depth review of the approach and interpretation of physical examination of the emergency patient.*

MD Kittleson: Signalment, history and physical examination. In MD Kittleson, RD Kienle (Eds.): *Small animal cardiovascular medicine*. 1998, Mosby, St Louis, *Chapter describing physical examination with an emphasis on cardiovascular evaluation. Excellent technique of auscultation and description of murmurs.*

MI Kotlikoff, JR Gillespie: Lung sounds in veterinary medicine. Part I. Terminology and mechanisms of sound production. *Comp Cont Educ Pract Vet*. **5**, 1984, 634, *Although an older publication, one of the best reviews for describing and understanding lung sounds.*

* See the CD-ROM for a complete list of references

2 Chapter 2 Patient Triage*

D. Tim Crowe, DVM, DACVS, DACVECC, FCCM, NREMT-I, PI, CFF

2.1 KEY POINTS

- Triage means *to sort* and describes the process of prioritizing patient care when there is more than one patient requiring attention.
- In critical care medicine, patients requiring triage will include those arriving at the hospital on an emergency basis, hospitalized patients being transferred to the intensive care unit (ICU) from other areas of the hospital, and current ICU patients that deteriorate suddenly.
- Care of the seriously injured or critically ill patient requires a state of around-the-clock readiness of the facility, supplies, equipment, and staff.
- A “ready area” prepared with appropriate supplies and equipment that can be accessed readily is essential to stabilization of the critical patient.
- Triage is achieved by a primary survey based on the ABC approach, followed by a secondary survey.

* The author would like to dedicate this chapter in memory of Dr. John Anderson who died May 16, 2006. John and I taught some of the very first K-9 Emergency Care for Police Officers, and he continued teaching these throughout the country. Triage was one of John's favorite areas to teach.

2.2 INTRODUCTION

Care of the seriously injured or critically ill patient requires a state of around-the-clock readiness of the appropriate facility, supplies, equipment, and staff. Triage means *to sort* and describes the process of prioritizing patient care when there is more than one patient requiring attention. In critical care medicine patients requiring triage will include those arriving at the hospital on an emergency basis, hospitalized patients being transferred to the ICU from other areas of the hospital, and current ICU patients that deteriorate suddenly. Priority of need is based on the level of urgency required to ameliorate the global, tissue, and cellular consequences of their conditions. Optimal management 6 involves horizontal resuscitative care, a collective effort done by several individuals working together. This is in contrast to vertical resuscitative care, during which diagnostic and therapeutic tasks are completed in a step-by-step fashion. The latter is an effective way to deliver care but is slower and more burdensome to the practitioner.[1]

2.3 READINESS

There is good evidence that critically and multiply injured patients benefit from preplanned preparedness of facility and staff and a team approach with preplanned objectives (Box 2-1).[2,3] The ideal number of staff to have on a veterinary triage-resuscitation team has not been fully investigated. However, in the author's experience three to four is considered the minimum and is supported by research in human trauma centers[4]; these would include a veterinarian and at least two technical support staff. In the case of emergency patient assessment and stabilization, it is important that emergency team members be familiar with both their own roles and those of their colleagues.[2]

Resuscitation and stabilization of critical patients require rapid reestablishment of adequate oxygen delivery to the tissues. Research has shown that if cellular hypoxia of the gastrointestinal tract in dogs that are in hemorrhagic shock continues beyond *1 hour,* death from organ dysfunction and sepsis from gastrointestinal bacterial translocation and endotoxin absorption across the gut wall may occur a day to several days later.[5] Speed of resuscitation is also pivotal in saving the life of a pet with multiple injuries.[4] Therefore shock and tissue hypoxia must be reversed rapidly in the critically ill patient. To accomplish this, preplanning is imperative.

A "ready area" that is set up for immediate resuscitation is required.[1] The area should have excellent lighting and be organized in an "open system," where most items that may be needed are in the open and can be accessed readily. Suggested items for the "ready area" are listed in Box 2-1. It is highly recommended that the bag-valve and reservoir and the masks (small and large) be assembled for immediate use. A crash cart that is fully stocked and prepared for cardiopulmonary arrest should also be kept in the "ready area." Around-the-clock radiographic and ultrasonographic capabilities, laboratory capabilities, and continuous ICU care are required for most critically ill or injured patients. Laboratory assessment is mandatory and may include arterial and venous blood gas analysis, clinical chemistry levels (especially glucose), red and white blood cell counts, and urinalysis. Assessment of coagulation, serial hematocrits, and total plasma solids must be possible and readily available.

2.4 INITIAL ASSESSMENT AND CARE ON ARRIVAL

Appropriate treatment of the seriously ill or injured patient can be instituted only if the patient continues to be evaluated appropriately. A primary survey is performed initially; this is followed by a secondary survey once the patient is considered relatively stable. Pain control is also achieved early and effectively. Analgesic and sedative drugs with significant hemodynamic effects (such are acepromazine and medetomidine) should not be used in the critical patient. In addition, nonsteroidal antiinflammatory agents should be avoided until hemodynamic stability, 6
7 gastrointestinal function, and renal function have been evaluated. Opioids and benzodiazepines are the most frequently used sedative and analgesic drugs for the critically ill or injured patient. See Chapter 164, Analgesia and Constant Rate Infusions, for further discussion of analgesia of the critical patient.

2.4.1 Box 2-1 Guideline of Items Required for the Resuscitation (Ready) Area

2.4.1.1 General

Surgical gurney: a stretcher that has height adjustments with wheels that can be locked

Small, medium, and large plastic (preferred) backboards

Surgical grade lighting (dual beam and 50,000 lumens)

2.4.1.2 CPR

Crash cart with ready-to-use clear endotracheal tubes, laryngoscope, and assorted blades

Drugs for resuscitation (e.g., epinephrine, calcium, atropine, lidocaine, dopamine)

2.4.1.3 Oxygen Administration

Oxygen source (with a regulator or flow meter attached to an E cylinder and caddy, or anesthesia machine with Y connector or in-line wall-mounted oxygen)

Resuscitators (Ambu bag or breathing circuit that allows manual ventilation): infant, pediatric, and adult sizes, all with reservoirs

Small, medium, and large preassembled Crowe oxygen collars

Infant, pediatric, and adult nasal cannulas

Large and small cone masks

Positive end-expiratory pressure valves that can be attached to resuscitation device

Mechanical ventilator set up and ready to be connected

2.4.1.4 Fluid Resuscitation

Blood draw and IV catheter placement cart

Infusion pumps and syringe pumps

Fluid and towel warmer

Lactated Ringer's solution, normal saline, Plasmalyte, or Normosol R

Whole blood and plasma and synthetic substitutes (Oxyglobin, hetastarch, dextran)

2.4.1.5 Miscellaneous

Doppler blood flow detector and blood pressure cuffs

Suction units (two ideally) with reservoirs, with one connected to a sterile suction trap

Duct tape to immobilize patients

Warming device (blanket, water-circulating heating pad, warm air flowing device)

Clippers and clipper blades

Pleur-evac (for pleural space continuous evacuation)

Portable ultrasonography unit

2.4.1.6 Wound Management

Sterile towels to pack wounds and wrap patients that have multiple wounds

Wet saline dressings and surgical scrub for all preparations

Other dressing materials and bubble wrap and newspaper for splints

2.4.1.7 Emergency Surgical Procedures

Chest-crack surgical pack; infant, medium, and adult Balfour retractors

Tracheostomy tray

Vascular cutdown tray

Chest tube tray

Peritoneal lavage tray with several lavage catheters

Wound (laceration) tray

2.4.2 Primary Survey

The primary survey of a critical patient should follow the ABC approach.[1]

2.4.2.1 A = Airway

The primary survey begins with assessment of the patient's airway. This includes early, aggressive, nonconfining oxygen supplementation. This may be achieved by directing an oxygen source at the animal's nose or mouth (flow-by oxygen), via a face mask or with a clear plastic hood.[6] If respiratory function is compromised or absent, bag-valve-mask ventilation should be instituted immediately while preparations are made to intubate. Preoxygenation of patients with the bag-valve-mask before attempting intubation may reduce the incidence of cardiopulmonary arrest. Orotracheal intubation (with or without anesthesia) is indicated if the airway is obstructed or if the patient has an absent gag reflex. If an orotracheal tube cannot be placed because of obstruction, emergency tracheotomy or cricothyroidotomy is indicated.

2.4.2.2 B = Breathing

Once a patent airway is established, the animal's breathing efforts are observed. If there are none visible or only weak breathing efforts evident, the animal should be intubated (if this has not already been done) and manual positive pressure ventilation initiated immediately. If the animal is completely unconscious the head of the animal should not be elevated and intubation should be attempted with the animal in lateral or dorsal recumbency. Following intubation manual positive-pressure ventilation is initiated immediately.

If the animal is breathing spontaneously, the adequacy of oxygenation and ventilation is best assessed by careful visualization and auscultation. In some cases such emergency measures as an emergency tracheotomy and pleural space decompression must be completed rapidly. If the animal is breathing spontaneously, the adequacy of oxygenation should be ascertained by pulse oximetry and arterial blood gas measurement. These assessments generally are performed as part of the secondary survey.

2.4.2.3 C = Circulation

Major visible hemorrhage is stopped by applying pressure manually and with compression dressings. Occasionally direct exposure and temporary vascular occlusion must be done to stop severe hemorrhage that does not respond to manual pressure and dressings. In these cases, subsequent ligation or repair of the bleeding vessels will be required.

Tissue perfusion is assessed by observing the level of consciousness, pulse strength, mucous membrane color, capillary refill time, jugular vein distention, and heart rate. When palpable pulses and audible heart beat are absent, cardiac arrest should be assumed and cardiopulmonary resuscitation (CPR) started. If intubation and manual ventilation was not begun previously, it should be initiated immediately in addition to chest compressions and appropriate resuscitative drug administration (see Chapter 4, Cardiopulmonary Resuscitation). Obtundation, pale mucous membranes, slow capillary refill times, and poor jugular vein distention are all indicative of poor perfusion or shock. Arterial blood pressure and assessment of jugular vein distention and speed of filling and emptying is also used to help determine global perfusion, and rapidly determined point-of-care serial lactate, PvO_2, and base excess values will aid in further assessment of tissue perfusion. Venous partial pressure of oxygen (PO_2) has been found by the author to be an effective means of assessing perfusion effectiveness. PvO_2 measurements below 35 mm Hg are considered an indication of hyperperfusion. The use of Doppler blood flow monitoring, with the probe placed on the palmar arterial arch (or even the surface of the eye in the arrested or near arrested unconscious patient) has been shown to be a very effective is assessing circulatory function.

The three main causes of shock are hypovolemia, vasodilation, and cardiac failure, and patients may suffer from more than one of these problems. Most shock states in the trauma patient result from blood loss, with secondary causes associated with plasma-fluid loss, third space loss within edema associated tissues and pain over time. In contrast, critically ill patients may be hypovolemic due to severe dehydration or third space fluid losses (especially losses into the gastrointestinal tract). Vasodilation is most commonly a consequence of a severe systemic inflammatory response, with or without sepsis. Anaphylaxis and ischemic-reperfusion injury can also cause generalized vasodilation. Vasodilatory shock may cause hyperemic mucous membranes and bounding pulses, but most patients with vasodilatory shock have concurrent hypovolemia and will demonstrate signs more consistent with hypovolemic shock before adequate fluid resuscitation. Primary cardiac disease is the most common cause of cardiogenic shock.

Intravenous access ideally is secured while assessment of the ABCs is being performed. Catheters will be more easily placed when a small opening in the skin is made to provide easier access to the vein. If the vein is collapsed then a mini-cutdown procedure is recommended. This is commonly done with an 18- to 20-gauge needle; the bevel of the needle is used as a small blade and a ¼-inch incision is made over the vein and a curved small-tipped hemostat is used to isolate and stabilize the vein for catheter introduction. Immediate fluid resuscitation is indicated in all shock patients other than those suspected to have cardiac failure. In most cases fluid resuscitation aims to restore normal cardiovascular parameters. In cases of active internal hemorrhage, a less aggressive fluid resuscitation approach such as “hypotensive resuscitation” may be considered[7] (see Chapter 65, Shock Fluids and Fluid Challenge).

2.4.2.4 D = Disability

The ABCs of triage have been extended to ABCDE. The *D* stands for disability. The animal's level of consciousness and ability to move and feel pain in all four limbs are assessed. The letters AVPU can be used for quick categorization: *A* = alert, *V* = responsive to verbal stimulation, *P* = responsive to painful stimulation, and *U* = unresponsive to painful stimulation. Seizure activity requires immediate anticonvulsant therapy and should be controlled before starting the primary survey. Research again has shown that the most important emergency triage drug to use in virtually all head or spinal cord emergent or critical conditions is supplemental oxygen. 7

8

2.4.2.5 E = External Assessment

External assessment is particularly relevant to the acute trauma victim. The entire animal is evaluated for bleeding (including from orifices), lacerations, punctures, abrasions, contusions, significant swelling, crepitus, pain on palpation, obvious hernias, open fractures, angulations, or deformities. The umbilical region is examined for periumbilical ecchymosis (Cullen sign), which may indicate hemorrhage in the peritoneum or retroperitoneum.

2.4.3 Secondary Survey

Once the primary survey is complete and appropriate emergency therapy has been instituted, a secondary survey is performed. This includes a full physical examination, measurement of arterial blood pressure, assessment of jugular vein distention and relaxation time, and evaluation of emergency blood work results. Ideally emergency blood work should include hemoglobin levels, or packed red blood cell volume, total protein, blood glucose, electrolytes, arterial and venous blood gas, and lactate measurements. Abnormalities should be managed as indicated.

Oxygenation is assessed with pulse oximetry or arterial blood gas analysis. Arterial partial pressure of oxygen (PaO_2) of less than 80 mm Hg (pulse oximeter saturation [SpO_2] <95%) is indicative of hypoxemia, and a PaO_2 of less than 60 mm Hg (SpO_2 <90%) indicates severe hypoxemia. If severe hypoxemia persists despite oxygen therapy and management of primary disease processes (evacuation of pleural space disease, for example), mechanical ventilation is indicated. Ventilatory ability is evaluated best by measurement of the partial pressure of carbon dioxide in arterial or venous blood (PCO_2). PCO_2 levels of greater than 45 mm Hg indicate hypoventilation, and PCO_2 levels greater than 60 to 70 mm Hg despite treatment of the primary disease process is an indication for mechanical ventilation.

2.5 TRIAGE

2.5.1 Hospital Arrival

When patients present to the hospital on an emergency basis, a quick history is obtained from the owner or agent of the pet. The team must be ready to move the animal from the transporting vehicle into the hospital. A backboard made of Plexiglas or plastic or a commercially available stretcher can be very useful, as can a cart or gurney. Initial questions include “What happened?” “When?” “What was done?” and “Does the animal have any current health problems?” A more detailed history can be obtained later, once the animal has been assessed and stabilized. Rapid assessment and triage should be completed within the first few minutes of arrival in all critically ill or injured animals.[1] It is recommended when possible to have the owners accompany the pet to the ready resuscitation area in the treatment part of the hospital and, in some cases, to have them sit in a chair while early interventions are being accomplished (jet flow-by oxygen, auscultation and palpation, clipping for IV catheter placement). As these are done the owner can be asked further questions such as “Did you see the accident?” “Is he allergic to any medications? When was the last time he ate? Are there any other medical conditions that he has?” This also allows the owner to see where the pet has been taken and that there are others working to help in the pets care. Seeing positive things being done for the pet will help relieve stress for the owner. In some cases, when help is very scarce, the owner may have to assist the veterinarian (recognized as not ideal but sometimes this is necessary although it does carry additional risks).

When multiple patients require attention simultaneously, those that are not ambulatory are considered of the highest priority. Those able to walk under their own power but have obvious problems with breathing, circulation, or other significant problems would receive the second highest priority. Patients that are ambulatory with no obvious problems would be left as the lowest priority.

2.5.2 Safety

Ideally gloves are worn when contacting the patient; this is to protect both the patient and the caregiver. Trauma patients commonly are covered in blood, and this may be the patient's own blood or that of an injured person who has handled the animal. To prevent transmission of hepatitis, human immunodeficiency virus, or nosocomial infections, two pairs of latex gloves or one pair of plastic nitrile gloves should be worn. Other precautions such as wearing protective eyewear should also be considered.

Other safety risks should also be assessed and action taken accordingly. Muzzles should be placed on conscious dogs, and distressed cats should be wrapped in a towel. Cats can also be left in the transport carrier or the box they came in. Oxygen therapy is of particular importance in patients with obvious respiratory distress. Jet flow-by oxygen is most commonly used initially; the stream of oxygen can be directed down the mouth of open-mouth–breathing patients. If cats are too distressed to be handled, high rates of flow-by oxygen can be directed into the carrier. Within a minute or two the concentration of oxygen will be close to 100%. If high-percentage supplemental oxygen alone does not ameliorate the signs of severe respiratory distress, positive-pressure ventilation is indicated.

If cases are oxygen responsive, a Crowe oxygen collar can be placed on them or a nasal or bilateral nasal catheter or cannula can be inserted and oxygen provided at a rate of 100 to 200 ml/kg/min (which provides from 40% to 80% oxygen in most cases).

2.6 SPECIAL CONSIDERATIONS FOR THE HOSPITALIZED PATIENT

When the hospitalized patient is brought to the ICU or the ICU patient suddenly deteriorates and requires evaluation, some unique considerations arise that are not relevant to emergency patient triage. A review of the fluid and drug therapy for that patient is important. Overall fluid balance (fluid intake versus fluid output) should be assessed during the entire hospitalization in case substantial fluid deficits or excesses exist. Drug therapies should be scrutinized for possible interactions, incorrect dosages, and incorrect route of administration. Incorrect administration of drugs such as potassium chloride and insulin can be a cause of unexpected collapse and cardiac arrest. Lastly, it is important to perform a full primary and secondary survey on these patients, including a review of the emergency blood work. 8
There can be a temptation to skip much of this procedure because the animal has already undergone recent physical 9
examinations and diagnostic tests. Critically ill patients can change rapidly; patient deterioration or failure to improve despite therapy warrants complete reassessment every time.

2.7 SUMMARY

The ultimate objective of the triage process is to identify those patients that require the most urgent medical attention. Adequate patient care requires the appropriate facilities, equipment, and staff, with 24-hour availability. A predesignated, appropriately prepared "ready area" will allow provision of urgent, possibly lifesaving care to the unstable patient. A standard approach to a primary and secondary survey will provide an efficient method of patient assessment, with minimal risk of missing important clinical abnormalities. In addition to these objectives, clear client communication is vital to ensure that owners fully understand the nature and prognosis of all disease processes identified in their pets.

2.8 SUGGESTED FURTHER READING*

DT Crowe: A general approach to emergency patients. *Vet Med*. **98**, 2003, 777, *A good overview of treating emergency veterinary patients*.

DT Crowe: Clinic and staff readiness: the key to successful outcomes in emergency care. *Vet Med*. **98**, 2003, 760, *One of the few articles specifically addressing emergency preparedness in veterinary medicine*.

DT Crowe: Triage and trauma management. In RJ Murtaugh (Ed.): *Veterinary emergency and critical care medicine*. 1992, Mosby, St Louis, *An excellent chapter on management of the trauma patient; recommended reading for the new emergency veterinarian*.

* See the CD-ROM for a complete list of references

3 Chapter 3 Survival Prediction Index

Lesley G. King, MVB, DACVECC, DACVIM

3.1 KEY POINTS

- Scoring systems such as the SPI are used to categorize patients into groups with similar severity of disease, which allows risk stratification of groups of patients for clinical research studies.
- Ideally, scoring systems should be independent of the diagnosis and therefore applicable to any patient and any disease, and they should use readily available information that can be collected early during hospitalization,
- The Survival Prediction Indices (SPI 1 and 2) were developed and validated for use in dogs admitted to the intensive care unit.

3.2 INTRODUCTION

A variety of systems that place a numeric score on the severity of disease are used in human critical care,[1-4] and similar systems are being developed for use in the small animal intensive care unit (ICU).[5-12] Equations have also been developed for large animals but are beyond the scope of this chapter.[13-16] Some systems globally classify the degree of physiologic derangement regardless of the diagnosis, and some are designed to be applied to specific situations, for example peritonitis or trauma. These systems have the common goal of attempting to objectively classify the severity of disease; in other words, to predict the outcome within a given patient population.

3.3 APPLICATIONS AND INDICATIONS FOR SCORING SYSTEMS

All scoring systems are developed for the same purpose: to categorize patients into groups with similar severity of disease. This is particularly important for risk stratification of groups of patients for clinical research studies. Clinical research trials are necessary to advance our understanding of the pathophysiology and management of disease. However, small animal patients with naturally occurring disease are usually a mixture of ages and breeds, may be brought for treatment at different stages of the problem, may have received a variety of treatments, and may have multiple concurrent diseases in addition to the problem being studied.

Although research animals with experimentally induced disorders are important models of naturally occurring disease in both humans and animals and provide a much more homogeneous population, the use of these animal models has certain disadvantages. In particular, experimentally induced models of disease may be expensive and time consuming to produce, and the disorders may not be identical to those that occur in clinical patients. Thus, results from experimental studies may not apply directly to clinical cases.

Our ability to draw conclusions from clinical trials of management techniques or new therapies is therefore often hampered by our inability to define homogeneous patient populations that can be compared. For example, if we were testing a new drug for treatment of dogs with autoimmune hemolytic anemia, the results might be difficult to interpret unless the test group has been proven to have the same type and severity of hemolysis, the same degree of systemic illness, and therefore the same risk of mortality as the standard treatment group. This problem can be addressed partially by developing an index for scoring the severity of disease, which attempts to place a numeric value on the degree of illness in the patients included in the clinical trial. Patients can then be categorized into groups with a similar severity of disease, which then allows comparison of groups for clinical trials.

Similarly, these scoring systems can also be used if a specific test result is being studied to determine its relationship to the severity of disease. They may also have some utility for triage of patients to objectively and prospectively allocate resources of staffing and equipment. Objective characterization of the severity of disease also allows quality control and comparison of actual outcomes between institutions and within institutions over time.

Ideally, such indices should be independent of the diagnosis and therefore applicable to any patient and any disease. In addition, the ideal prediction index should use readily available information that can be collected early during hospitalization, before beginning the clinical trial. If it can be shown that the severity of illness is initially statistically similar in two groups that are then treated differently, the results of the clinical trial carry more weight.

3.4

EVALUATING THE PREDICTIVE ACCURACY OF SEVERITY-OF-DISEASE SCORING SYSTEMS

The statistical accuracy of severity-of-disease scoring systems can be assessed by evaluation of the area under the receiver operating characteristic curve, sensitivity and specificity, odds ratios, or positive and negative predictive indices. The predictive accuracy of logistic regression equations is usually estimated using receiver operating characteristic (ROC) curves, which demonstrate the tradeoff between the true-positive rate (sensitivity) and the false-positive rate (1 minus specificity) at varying predictive cut-points. The area under the ROC curve (AUC) represents the probability that a randomly selected “survivor” has a larger predicted probability of survival than a randomly selected “nonsurvivor,” and is therefore a measure of the predictive value of the equation. The higher the AUC value (closer to 1), the more accurate is the equation. In human outcome prediction equations, AUC values commonly are obtained as high as 0.85 to 0.90.

3.5

SURVIVAL PREDICTION INDEX: THE PILOT STUDY

The survival prediction index (SPI) was developed as a method of scoring the severity of disease of critically ill dogs in the ICU.[5-7] The system comprises parameters that are independent of the diagnosis, and are part of the routine monitoring and evaluation of ICU patients. Data for this calculation can therefore be collected early during hospitalization and before interventions being tested in clinical trials.

A pilot study was conducted initially to develop an SPI using data from 200 dogs admitted to the ICU at the Veterinary Hospital of the University of Pennsylvania.[5] The SPI was calculated by logistic regression analysis, using clinical parameters collected within the first 24 hours after admission to the ICU. For the pilot study, all of the data were collected by one person. The parameters were chosen to reflect the function of vital organ systems, the severity of underlying physiologic derangement, and the extent of physiologic reserve (Box 3-1).

Some parameters were measured serially as part of routine intensive monitoring, for example rectal temperature, heart rate (HR), respiration rate (RR), mean arterial pressure (MAP), oxygen saturation (SaO_2), packed cell volume (PCV), total solids (TS), and glucose. Other parameters such as age, body weight, white blood cell count (WBC), creatinine, albumin, bilirubin, and bicarbonate were usually measured only once within the 24-hour study period. If serial measurements of a parameter were available, the most abnormal value (most deviated above or below the normal range) was used. In postoperative patients, the initial body temperature was usually low, and then increased to a plateau over the first few hours. In these cases, the plateau rather than the admission temperature was recorded. Based on clinical observation, animals were assigned a score of 1 or 2 if they had clinical evidence of central

nervous system disease, and 0 if they were thought to be neurologically normal. Similarly, animals were assigned a score of 1 if they had medical illness, and 0 if they had surgical disease. Finally, animals were given a score of 5 if they had chronic illness, and 0 if their disease was acute. Chronic illness was diagnosed if there was evidence of failure of a major organ persisting for longer than 1 month, for example, chronic renal failure, chronic hepatic insufficiency, or chronic congestive heart failure; systemic neoplasia such as lymphosarcoma or hemangiosarcoma; any form of immunosuppression including chemotherapy, immunosuppressive drugs, hyperadrenocorticism, or diabetes mellitus; or congenital disease that may lead to compromised organ function, such as brachycephalic airway conformation, immune deficiency, portosystemic shunt, or cardiovascular anomalies. Outcome was defined 10
as alive or dead after 30 days, with day 1 defined as the day of admission to the ICU. Outcome was determined by 11
reexamination or by a telephone conversation with the owner.

3.5.1

Box 3-1 Parameters Recorded Within 24 Hours of Admission to the Intensive Care Unit

SPI	SPI 2
Age (years)	Age (years)
Body weight (kg)	Respiration rate (breaths/min)
Rectal temperature (°F)	Mean arterial pressure (mm Hg)
Heart rate (beats/min)	Service of entry (surgical or medical)
Respiration rate (breaths/min)	Packed cell volume (%)
Mean arterial pressure (mm Hg)	Creatinine (mg/dl)
Oxygen saturation SaO_2 (%)	Albumin (g/dl)
Neurologic disease (Y/N)	
Service of entry (surgical or medical)	
Chronic disease (Y/N)	
Packed cell volume (%)	
Total solids (g/dl)	
Glucose (mg/dl)	
White blood cell count (cells/mm^3)	
Creatinine (mg/dl)	
Albumin (g/dl)	
Bilirubin (mg/dl)	
Bicarbonate (mmol/L)	

Logistic regression analysis resulted in the following linear equation:

$$
\begin{aligned}
\text{logit}(\text{P}) = {} & -19.9676 + 0.1537(\text{rectal temperature}) \\
& +0.00742(\text{MAP}) - 0.0144(\text{BW}) - 0.00164(\text{HR}) \\
& +0.00423(\text{RR}) + 0.0668(\text{SaO}_2) + 0.0123 \\
(\text{bicarbonate}) & - 1.2567(\text{neurologic disease}) \\
& - 0.8375(\text{creatinine}) + 0.0350(\text{PCV}) - 0.0403 \\
(\text{WBC}) & - 0.2732(\text{albumin}) + 0.5082(\text{TS}) \\
& - 0.1163(\text{age}) + 0.00280(\text{glucose}) - 0.2114 \\
(\text{bilirubin}) & - 0.9294(\text{medical / surgical}) \\
& - 0.0796(\text{acute / chronic})
\end{aligned}
$$

The numeric values are entered into the linear equation to give a value for logit P, which is the log odds of survival. An exponential equation is used to solve for P, the predicted probability of survival.

$$
\text{P}(\text{SPI}) = \frac{e^{\text{logit}(p)}}{\left[1 + e^{\text{logit}(p)}\right]}
$$

The predicted probability (SPI) value thereby obtained is within the range of 0 to 1, with 0 indicating the most severe disease, and 1 indicating no mortality risk. The AUC for this equation, calculated using data from the 200 dogs used to develop the equation, was 0.89, suggesting reasonable predictive accuracy for this particular patient population.

3.6 SURVIVAL PREDICTION INDEX 2: THE MULTICENTER TRIAL

The first objective of the multicenter study was to test prospectively the accuracy of the SPI in a larger cohort of dogs admitted to various ICUs.[6] The investigators wished to include critically ill dogs in a variety of locations, and to use data collected by a variety of personnel. A second objective, using the multicenter data, was to generate an improved SPI, the SPI 2. Lastly, using estimation and validation samples, the predictive accuracy of SPI 2 was to be tested for future use.

Data were collected from dogs admitted to small animal ICUs at four locations: University of Pennsylvania, Tufts University, University of Minnesota, and VCA Veterinary Referral Associates in Gaithersburg, Maryland. Six hundred and twenty-four dogs were included, with the same parameters recorded as with the pilot study, within 24 hours of ICU admission. Data were collected by a variety of individuals including the investigators, veterinary nurses, and veterinary students. The overall survival rate was 61.1%, with 381 of 624 dogs alive after 30 days. There was no significant difference in survival rate among the sites. The dogs were divided randomly into an estimation group (n = 499) and a validation group (n = 125).

3.6.1 Prediction of Outcome in the New Sample, Using the Model From the Pilot Study

The AUC for the pilot SPI model, using the original group of dogs, was 0.89. When it was tested using data from the new (estimation) group of dogs (n = 499), the AUC decreased to 0.723. The high AUC value previously reported was positively biased because it was calculated using the same data that were used to generate SPI. Additionally, it is possible that there were differences between the original population of test dogs and those included in this multicenter study.

3.6.2 Using the New (Multicenter) Sample to Create a New Survival Prediction Index

The data from this new (multicenter) group of dogs were used to perform a new logistic regression analysis, thereby reestimating the parameters to create a new SPI, the SPI 2. In the full model, the AUC obtained for the estimation sample (n = 499) was 0.773, while that of the validation sample (n = 125) was 0.72. Then a backward elimination procedure was used to sequentially eliminate variables that had a minimal impact on the accuracy of prediction of survival, thereby obtaining a more manageable model with fewer variables, while retaining the same level of discrimination in predicting outcome. Variables that were eliminated included temperature, body weight, heart rate, neurologic status, SaO_2, bicarbonate, white blood cell count, total solids, glucose, bilirubin, and chronicity of disease. The AUC for the reduced model in the estimation sample was 0.76, and in the validation sample was 0.68, which showed minimal loss in predictive accuracy. Thus, the new SPI 2 equation is as follows:

$$\begin{aligned}\operatorname{logit}(P) = {} & 0.3273 + 0.0108(\mathrm{MAP}) - 0.0101(\mathrm{RR}) \\ & - 0.2183(\text{creatinine}) + 0.0164(\mathrm{PCV}) \\ & + 0.3553(\text{albumin}) - 0.1184(\text{age}) \\ & - 0.8069(\text{medical} / \text{surgical})\end{aligned}$$

where medical/surgical ratio is equal to 1 if the animal is from a medical service and 0 if it is from a surgical service. The numeric values are entered into the linear equation to give a value for logit P, which is the log odds of survival. The exponential equation is used to solve for P, the predicted probability of survival.

$$P(\text{SPI } 2) = \frac{e^{\operatorname{logit}(p)}}{1 + e^{\operatorname{logit}(p)}}$$

The predicted probability (SPI 2) value falls within the range from 0 to 1, with 0 indicating the most severe disease and 1 indicating no mortality risk.

The optimal cut-point was derived from the ROC curve using the ratio of the nonsurvival-to-survival rates, which in the sample from the University of Pennsylvania was 0.389/0.611, or 0.637. This tangent line corresponds to a prediction index cut-point of approximately 0.50. The estimated positive and negative predictive values (95% confidence interval) at this (optimal) cut-point are 73.4% (68.9% to 77.5%) and 66.2% (59.0% to 72.7%), respectively. The estimated sensitivity and specificity at this cut-point are 82.7% (78.4% to 86.3%) and 53.1% (46.6% to 59.5%), respectively.

3.7 SCORING SYSTEMS IN THE HUMAN ICU

Numerous similar studies have been published and the findings are in routine use in humans to classify patients into 11
groups for clinical trials.[1-14] The most commonly used system in human medicine is the acute physiology, age, 12
chronic health evaluation (APACHE) scoring system.[1,2] In studies of human patients using APACHE scoring, AUC values as high as 0.90 are commonly obtained. The numbers of human patients used to develop those equations were

much larger than can easily be collected by veterinary researchers. For example, data were accrued from more than 17,000 patients for development of the APACHE III scoring system.[2]

The APACHE III scoring system is similar to the SPI 2 because it includes MAP, RR, hematocrit, and creatinine and albumin concentrations. Some variables that were found not to be significant in the study dogs are still included in the APACHE system, specifically HR, temperature, partial pressure of oxygen, and alveolar-arterial oxygen gradient, WBC count, and bilirubin and glucose concentrations. Other variables that are included in the APACHE scoring system but that were not tested as part of the SPI 2 study include urine output, blood urea nitrogen level, and serum sodium concentration.

3.8 USING SPI And APACHE IN PATIENT SUBSETS

Preliminary studies of the SPI 2 suggest that it may be more accurate in dogs admitted to the ICU with a medical problem (AUC = 0.75) than with surgical admissions (AUC = 0.70).[6] However, there were approximately twice as many medical admissions in this study as surgical admissions, which may have contributed to this difference. Additional studies are needed to further explore this question in veterinary patients. Similarly, in human medicine the APACHE system is not as accurate in patients treated for trauma-induced illness, compared with those who have medical conditions.[17] The authors of that study hypothesized that the prediction for previously healthy humans who had acute trauma would have been more accurate if it had included an anatomic component similar to that suggested in the animal trauma triage scoring system.[9]

3.9 SERIAL USE OF THE SPI On Sequential Days Of ICU Hospitalization

In another study, the utility of serial estimations of the SPI on days 1 and 3 of ICU hospitalization was evaluated.[7] It was hypothesized that data obtained later during hospitalization, closer to the time of the actual outcome, might provide a more accurate prediction that would be more clinically useful for decision making in specific patients. In a group of 64 dogs, the AUC was higher using day 3 measurements (AUC = 0.70) than that obtained using day 1 measurements (AUC = 0.65), but the increase in the AUC value was not statistically significant.[7]

3.10 LIMITATIONS OF SCORING SYSTEMS

Much debate centers around the potential use of these scoring systems for prioritization of resources toward patients that have a greater predicted chance of survival. Although this approach may have debatable merit in human medicine from a moral perspective, the high AUC values in the scoring systems for humans suggest that there may be enough predictive accuracy to justify their use for this purpose. In contrast, the study of scoring systems in veterinary medicine is still in its infancy. The systems that have been developed were studied in relatively small numbers of animals. Many have not yet been adequately validated, or if they have been validated, they do not give a level of predictive accuracy that compares with the systems available for human medicine. In individual animal patients, therefore, it is arguable whether the veterinary systems provide additional information over that obtained by the thoughtful evaluation by an experienced clinician. Veterinary indices should be used to statistically predict percentages of survival in groups of patients, rather than in individual animals. The lower AUCs for the veterinary scoring systems show that they provide sufficient predictive accuracy to be a valid tool for statistical analysis, but are insufficiently accurate to justify their use for decision making for individual animals. If outcome prediction equations were used to determine treatment for individual patients, there is a significant risk that an individual patient might be predicted to die, and therefore be euthanized, but instead would have survived; alternatively, another patient might be treated based on a score that predicts survival, but might die. Much further study needs to be done to refine these systems, to include many more patients in both estimation and validation samples, and to generate more accurate equations and scoring systems.

3.11 SUGGESTED FURTHER READING*

1. LG King, H Fordyce, M Campellone, G Maislin: Serial estimation of survival prediction indices does not improve outcome prediction in critically ill dogs with naturally occurring disease. *J Vet Emerg Crit Care*. **11**(3), 2001, 183–189, *Study tested whether calculation of the SPI 2 on serial days of hospitalization would result in an improvement in our ability to predict outcome*.

LG King, MT Stevens, ENS Ostro, et al.: A model for prediction of survival in critically ill dogs. *J Vet Emerg Crit Care*. **4**, 1994, 85, *J Vet Emerg Crit Care* **5**, 1995, 6, Correction: *This paper reports our first veterinary attempt to develop a scoring system analogous to APACHE in dogs hospitalized in the ICU*.

LG King, JS Wohl, AM Manning, et al.: Evaluation of the survival prediction index as a model of risk stratification for clinical research in dogs admitted to intensive care units at four locations. *Am J Vet Res*. **62**, 2001, 948, *This study, we included data from dogs in multiple locations, and increased the number of patients included in the study, to validate the SPI 1 and then generate a new and shorter outcome prediction equation: the SPI 2*.

WA Knaus, EA Draper, DP Wagner, et al.: APACHE II: a severity of disease classification system. *Crit Care Med*. **13**, 1985, 818, *This is the original paper describing the APACHE II system for outcome prediction in people*.

WA Knaus, DP Wagner, EA Draper, et al.: The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. **100**, 1991, 1619, *The APACHE III system was developed to refine APACHE II, using a much larger number of human patients*.

* See the CD-ROM for a complete list of references

4 Chapter 4 Cardiopulmonary Resuscitation

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4.1 Key Points

- Successful cardiopulmonary resuscitation (CPR) requires a team that is well prepared and well equipped and communicates clearly during the course of the resuscitation.
- Causes of cardiopulmonary arrest fall into two categories, reversible and irreversible, with a vastly different prognosis for survival following CPR. It is appropriate to discuss “do-not-resuscitate” orders during hospital admission for patients with end-stage disease processes.
- Basic life support is the cornerstone of CPR and includes airway management, ventilation, and artificial circulation with external chest compression or internal cardiac compression.
- Advanced life support provides more specific interventions based on the circumstances of the arrest. Techniques include electroencephalogram monitoring, drug therapy, and defibrillation.
- Intensive care is often essential to minimize the impact of postresuscitation syndromes and improve chances for the long-term survival of a patient that has been resuscitated successfully.

4.2 INTRODUCTION

Proficiency in cardiopulmonary resuscitation (CPR) is essential for every veterinarian practicing in an emergency or critical care setting. Given the nature of the patient population in these environments, cardiopulmonary arrest is not uncommon. In many cases, this represents a situation in which intervention can be lifesaving. Proper technique and timing may result in the return of spontaneous circulation and can make the difference between life and death. Guidelines for CPR in humans exist, with recommendations determined from an evidence-based review of clinical and experimental studies by an international consensus committee.[1] Unfortunately, no large-scale clinical studies of CPR have been done in veterinary patients, and recommendations for performing CPR in animals have been extrapolated from human guidelines, as well as experimental studies with animal models.[2-4] In general, the prognosis for dogs and cats suffering cardiopulmonary arrest is poor, with less than 10% of patients surviving to hospital discharge; however, the possibility for a successful outcome does exist.[5,6] Despite prevailing conventional wisdom, a retrospective study indicates that most of the animals that do survive are neurologically intact at the time of hospital discharge.[7]

The likelihood of a successful outcome is increased when the resuscitation team is well prepared. Preparation begins with a well-defined and well-equipped resuscitation area. Ideally, this area should include a “crash cart” with supplies for venous access, airway management, and drug therapy, as well as monitoring equipment and a defibrillator (see Appendix 1). Oxygen should also be available, along with supplies necessary to perform manual ventilation, such as an Ambu bag, Bain circuit, or anesthesia machine. Essential to this preparation is the training of staff and their practice of specific roles and techniques in controlled situations. Each resuscitation team should have a defined leader to allow rapid decision making and clear communication during the resuscitation. Knowing the wishes of the owner before CPR is performed facilitates this process. This may be accomplished by establishing a resuscitation code at the time of hospital admission. In the author's hospital, a green code means all appropriate measures (including open-chest CPR) will be performed, a yellow code limits the team to closed-chest CPR only, and a red code means do not resuscitate. Finally, it is very useful to have a debriefing session following CPR to enhance the effectiveness of the team in future resuscitations.

4.3 CAUSES OF CARDIOPULMONARY ARREST

Cardiopulmonary arrest is defined as the complete cessation of effective circulation and ventilation. Common causes of cardiac arrest in veterinary patients include hypotension (secondary to hypovolemia, sepsis, or drug administration), hypoxemia (secondary to hypoventilation or lung disease), metabolic derangements (e.g., severe metabolic acidosis) and/or electrolyte abnormalities (e.g., hyperkalemia). Primary myocardial disease, which is a common cause of cardiac arrest in humans, is uncommon in veterinary patients. In some patients, full cardiopulmonary arrest is preceded by respiratory arrest, and chances for survival are markedly better if intervention is performed at this stage.[6] It is important to recognize that there are two subsets of patients that suffer cardiopulmonary arrest, those with reversible causes of arrest and those with disease processes that cannot be reversed. In the latter case, when the patient suffers cardiopulmonary arrest secondary to an end-stage disease, CPR offers little chance of a successful long-term outcome. In these cases, it is often appropriate to discuss the various resuscitation orders and the prognosis for recovery with the owner while obtaining a resuscitation code at the time of hospital admission.

4.4 BASIC LIFE SUPPORT

Basic life support encompasses the ABCs (airway, breathing, circulation) of CPR and is the foundation for all resuscitation efforts. Although many clinicians focus on drug therapy and defibrillation during resuscitation, establishing an airway, ensuring adequate ventilation, and generating blood flow via external chest compression or 14
internal cardiac compression must be performed quickly and properly to maximize the chance for recovery. 15
Traditionally, the ABC mnemonic has been followed for determining the order of intervention in basic life support. This often results in a delay in the initiation of chest compressions until the patient is intubated. Recent guidelines stress the importance of early initiation of chest compressions with minimal interruptions.[1] This concept may be extended to veterinary CPR, and although an airway should be established as soon as possible, chest compressions should not be delayed until after the patient is intubated.

4.4.1 Airway

An airway may be established rapidly by routine orotracheal intubation in most patients suffering respiratory or cardiopulmonary arrest (see Chapter 17, Endotracheal Intubation). This may be facilitated by the use of a laryngoscope and, if necessary, a stylet to stiffen the endotracheal tube. In some patients, the airway is obscured by saliva, gastric contents, blood, or edema fluid, and in these situations it is useful to have suction available to help clear the pharynx and aid in the visualization of the glottis. In other cases, the airway is obscured by pharyngeal swelling or a mass effect, and in many cases the patient may be intubated by directly palpating the larynx and then manually directing the tube into the glottis.

After the patient is intubated, the cuff should be inflated and the tube secured. Given the stress of an arrest situation, as well as the manipulation of the patient that occurs during CPR, it is not uncommon for the tube to be misplaced or to become displaced into the esophagus. Because of this, it is important to verify placement. This may be accomplished by direct visualization of the tube entering the larynx, palpation of the neck to ensure that the tube is not felt within the esophagus, auscultation of breath sounds, and proper chest wall movement during ventilation. End-tidal carbon dioxide ($ETCO_2$) monitoring is also useful to verify tube placement because tracheal gas should contain carbon dioxide (as long as blood flow to the lungs is present), but esophageal gas does not. If problems are encountered, the airway should be reevaluated and the patient should be reintubated if necessary. It is also important to verify that the cuff is inflated, because this is often a source of problems.

In rare instances, the patient cannot be intubated orotracheally. These situations include airway obstruction by foreign bodies that cannot be retrieved easily, massive pharyngeal swelling or mass effects, trauma with laryngeal or proximal tracheal disruption, and trismus or dental fixation devices that prevent normal jaw motion. When orotracheal intubation is not possible, an emergency tracheostomy is indicated (see Chapter 18, Tracheostomy). Should a tracheostomy tube not be available, a standard endotracheal tube may be used, with care taken not to place the tube distal to the carina, resulting in bronchial intubation. If necessary, the tube may be cut to a more appropriate length, with care taken not to cut the cuff balloon tubing.

4.4.2 Breathing

Once an airway is established, the patient should be ventilated manually with 100% oxygen. An Ambu bag is used most commonly, but a Bain circuit or anesthesia machine may also be used. The recommended respiratory rate during CPR is 10 to 24 breaths/min. Ventilation should be delivered to achieve normal chest wall excursions and, if possible, the airway pressure should be monitored and should not exceed 20 to 30 cm H_2O.

4.4.2.1 Box 4-1 Formulas for Myocardial and Cerebral Perfusion Pressure

- Myocardial perfusion pressure = Aortic diastolic pressure − Right atrial pressure
- Cerebral perfusion pressure = Mean arterial pressure − Intracranial pressure

If normal chest wall motion is not observed, problems with the endotracheal tube (esophageal intubation, uninflated cuff) should be investigated, because this is a common source of problems with ventilation during CPR. In the absence of airway-related problems, diminished chest excursions or decreased compliance suggests airway obstruction, severe parenchymal disease, or severe pleural space disease. Airway obstruction is not common, but it is possible for the endotracheal tube to become occluded by tracheal secretions, vomitus, or exudate. Severe parenchymal disease is often present in patients suffering respiratory or cardiopulmonary arrest, and possible manifestations include pulmonary edema, pneumonia, pulmonary contusions, inflammatory lung disease (acute lung injury [ALI] or acute respiratory distress syndrome [ARDS]), and neoplasia. Pleural space disease is also common, and ventilation may be limited by pleural effusion (hemothorax, chylothorax, hydrothorax, pyothorax), diaphragmatic hernia, or pneumothorax. Pneumothorax presents an especially challenging situation during CPR, because positive-pressure ventilation often exacerbates the condition and may result in tension pneumothorax. In this situation, air often is introduced faster than it can be removed by thoracocentesis, and cardiopulmonary arrest in an animal with pneumothorax is an indication for open-chest CPR.

Recommended rates for ventilation are commonly exceeded during CPR in humans.[8,9] The detrimental effects of relative hyperventilation during CPR have been documented in animal models of cardiac arrest, including elevated mean intrathoracic pressures compared with lower ventilation rates, and associated decreases in myocardial perfusion pressure and survival.[8,9] Although no studies exist in veterinary patients, it is almost certain that recommended ventilation rates are exceeded in this population as well, and this may have detrimental effects on the rate of successful resuscitation. Accordingly, it is important that the potential be recognized and hyperventilation avoided during CPR in veterinary hospitals.

4.4.3 Circulation

Blood flow during CPR is generated by external chest compression (closed-chest CPR) or by direct cardiac
compression (open-chest CPR). Regardless of the technique, the goal is to maximize blood flow to the coronary
and cerebral vascular beds. Coronary blood flow is driven by the myocardial perfusion pressure, which is
governed by the aortic diastolic pressure and right atrial pressure (Box 4-1). Myocardial perfusion pressure is an
extremely important variable in resuscitation, and it has been positively correlated to successful resuscitation in 15
both experimental models and in human patients.[10-11] Cerebral perfusion pressure is dictated by the mean aortic 16
pressure and intracranial pressure, and it is the major determinant of cerebral blood flow (see Box 4-1).

External chest compressions are performed more often than direct cardiac compressions in veterinary CPR, and the mechanism of blood flow varies depending on patient size. The cardiac pump model of blood flow is the most likely mechanism at work in small patients (<15 kg), with forward blood flow resulting from direct cardiac compression. The thoracic pump model of blood flow predominates in larger patients (<15 kg). In this model, forward blood flow occurs secondary to phasic changes in intrathoracic pressure generated by chest compressions.

External chest compressions are performed with the patient in lateral recumbency at a rate of 100 to 120 compressions per minute. The chest is compressed to a depth of 25% to 33% of the thoracic diameter with a 50:50 ratio of compression to relaxation. In small patients (<15 kg), the compressions are performed directly over the heart to maximize the effectiveness of the cardiac pump mechanism. In very small patients, such as puppies and cats, the entire thorax may be encircled, and the chest compressed with the operator's thumbs. For larger patients (>15 kg), compressions should be performed over the widest portion of the thorax. This results in the greatest change in intrathoracic pressure and maximizes flow via the thoracic pump mechanism. It should be noted that the cardiac output increases with higher compression rates, but it is difficult to maintain a rate of greater than 100 to 120 compressions per minute for an extended period. From a practical standpoint, the person performing compressions should stand so that the spine (as opposed to the sternum) of the patient is closest to the compressor. This position reduces the tendency of the patient to be pushed off the table while compressions are being performed. Additionally, having a small stepstool available allows for better leverage, resulting in better compressions with less fatigue.

Interposed abdominal compressions may be performed to increase the effectiveness of external chest compressions, resulting in increased venous return to the thorax in diastole and thus increasing forward flow.[12] Interposed abdominal compressions are an adjunct to standard CPR and may be considered in patients without known abdominal trauma, hemoperitoneum, or recent abdominal surgery when adequate personnel are available. With this technique, the abdomen is compressed during the relaxation phase of chest compressions, requiring coordination between the thoracic and abdominal compressors.

Although properly performed external chest compressions may generate approximately 20% of normal cardiac output, this may be diminished by factors that interfere with transmission of pressure or may result in collapse of the heart and great vessels. These conditions include pleural effusion, diaphragmatic hernia, pneumothorax, large-volume pericardial effusion and cardiac tamponade, and/or chest wall trauma resulting in rib fractures or disruption of the intercostal musculature. In addition, it can be difficult to achieve effective chest compressions in very large dogs (>50 kg). In these situations, direct internal cardiac compressions may result in significantly higher myocardial perfusion pressure than closed-chest CPR.[13] Open-chest CPR allows access to the descending aorta for aortic occlusion (cross-clamping), which directs blood flow to the coronary and cerebral circulation. Because of this, open-chest CPR should also be considered in cases of exsanguinating abdominal hemorrhage, when ongoing volume loss into the peritoneal cavity is likely to occur during CPR. Finally, because of its hemodynamic benefits, open-chest CPR should be considered in patients in whom closed-chest CPR has not resulted in return of spontaneous circulation within 2 to 5 minutes.

It should be noted that the decision to perform open-chest CPR should not be taken lightly, because the facilities and expertise to close the thoracotomy and treat the patient postarrest must be available. To perform open-chest CPR, the left lateral thorax is rapidly clipped and a brief aseptic preparation is applied. A lateral thoracotomy is performed at the fifth intercostal space extending from the dorsal fourth of the chest wall to a few centimeters from the sternum, avoiding laceration of the internal thoracic vasculature. The fifth intercostal space may be estimated by flexing the animal's elbow and drawing it caudally. Some veterinarians prefer to perform the entire thoracotomy with Mayo scissors, but a scalpel blade may also be used. Ventilation should be halted as the pleural space is entered, to avoid laceration of the lungs. Once the chest is open, a rib retractor may be used to increase exposure and facilitate manipulation of the heart. The heart is compressed manually at a rate of 100 to 120 compressions per minute, and this may be performed with either one or two hands depending on the size of the patient. An incision in the pericardium, below the level of the phrenic nerve, may also be performed to drain pericardial effusion, if present, and to facilitate manipulation and compression of the heart. As mentioned above, a lateral thoracotomy provides access to the descending aorta, which may be bluntly dissected and occluded with an aortic cross-clamp or with an encircling Penrose drain, red rubber drain, or Rumel tourniquet. Once spontaneous circulation resumes, the aortic occlusion may be removed gradually over 5 to 10 minutes. It is important to recognize that the chest may also be accessed via a transdiaphragmatic approach, and open-chest CPR should be performed immediately if an intraoperative arrest occurs during a celiotomy.

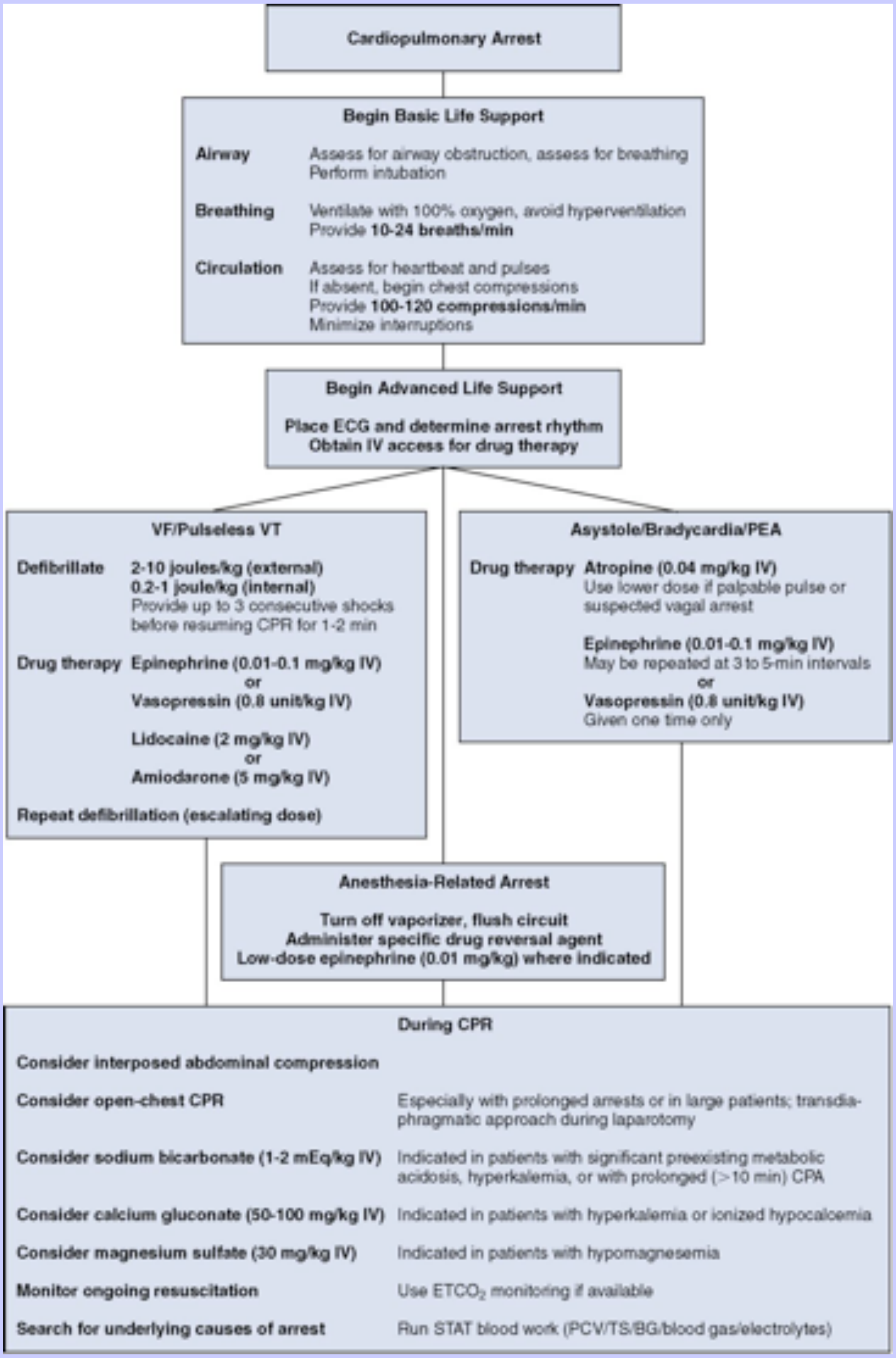
4.5 ADVANCED LIFE SUPPORT

Advanced life support extends the scope of CPR beyond ABC to include the Ds and Es of resuscitation: drug therapy, electrocardiographic (ECG) analysis, and electrical defibrillation. Drug therapy in CPR is aimed at improving the efficacy of basic life support techniques, as well as managing underlying problems associated with the arrest. ECG analysis allows for advanced life support interventions to be tailored to the underlying rhythm (Figure 4-1). Electrical defibrillation provides the only effective method of managing ventricular fibrillation and is also indicated in patients with pulseless ventricular tachycardia. Although advanced life support techniques are an essential component of CPR, properly performed basic life support is vital to the success of a resuscitation effort.

4.5.1 Establishing Access for Drug and Fluid Therapy

Obtaining access for drug and fluid therapy is vital during CPR. Either central or peripheral venous access
typically is established at the onset of resuscitation (see Chapters 61 and 63, Peripheral Venous Catheterization
and Central Venous Catheterization, respectively). Central venous access is ideal because circulation time of 16
drugs is better than with peripheral venous access.[14] Should peripheral veins be used, it is important to use large 17
flush volumes to deliver drugs more rapidly to the central venous circulation. Vessels are typically collapsed
during cardiopulmonary arrest, so rapid surgical cutdown is often necessary to secure venous access. When
performing a cutdown, it is important to make the incision large enough to easily dissect, puncture, and secure the 17
vessel of interest. Should venous access not be obtained, intraosseous catheterization may be performed using the 18
femur, proximal tibia, or humerus (see Chapter 62, Intraosseous Catheterization).

Figure 4-1 Algorithm for performing cardiopulmonary resuscitation in veterinary patients.


Cardiopulmonary Arrest
Begin Basic Life Support
Airway
Assess for airway obstruction, assess for breathing
Perform intubation
Breathing
Ventilate with 100% oxygen, avoid hyperventilation
Provide 10-24 breaths/min
Circulation
Assess for heartbeat and pulses
If absent, begin chest compressions
Provide 100-120 compressions/min
Minimize interruptions
Begin Advanced Life Support
Place ECG and determine arrest rhythm
Obtain IV access for drug therapy
VF/Pulseless VT
Defibrillate
2-10 joules/kg (external)
0.2-1 joule/kg (internal)
Provide up to 3 consecutive shocks before resuming CPR for 1-2 min
Drug therapy
Epinephrine (0.01-0.1 mg/kg IV)
or
Vasopressin (0.8 unit/kg IV)
Lidocaine (2 mg/kg IV)
or
Amiodarone (5 mg/kg IV)
Repeat defibrillation (escalating dose)
Asystole/Bradycardia/PEA
Drug therapy
Atropine (0.04 mg/kg IV)
Use lower dose if palpable pulse or suspected vagal arrest
Epinephrine (0.01-0.1 mg/kg IV)
May be repeated at 3 to 5-min intervals
or
Vasopressin (0.8 unit/kg IV)
Given one time only
Anesthesia-Related Arrest
Turn off vaporizer, flush circuit
Administer specific drug reversal agent
Low-dose epinephrine (0.01 mg/kg) where indicated
During CPR
Consider interposed abdominal compression
Consider open-chest CPR
Especially with prolonged arrests or in large patients; transdiaphragmatic approach during laparotomy
Consider sodium bicarbonate (1-2 mEq/kg IV)
Indicated in patients with significant preexisting metabolic acidosis, hyperkalemia, or with prolonged (>10 min) CPA
Consider calcium gluconate (50-100 mg/kg IV)
Indicated in patients with hyperkalemia or ionized hypocalcemia
Consider magnesium sulfate (30 mg/kg IV)
Indicated in patients with hypomagnesemia
Monitor ongoing resuscitation
Use ETCO2 monitoring if available
Search for underlying causes of arrest
Run STAT blood work (PCV/TS/BG/blood gas/electrolytes)

Another technique that is extremely useful is intratracheal drug administration. This can be performed immediately after intubation, minimizing the delay that often occurs while venous access is established. With this technique, the drug dosage is doubled, diluted to a volume of 2 to 5 cc, and is administered through a red rubber catheter that has been advanced past the tip of the endotracheal tube to the approximate level of the carina. This exposes the drug to the large surface area of the lung and pulmonary circulation, where it is absorbed and delivered to the central circulation. With the notable exceptions of sodium bicarbonate and calcium, most common CPR drugs may be administered by this route. It should be noted that intracardiac drug administration is not recommended because of risks of lacerating lung tissue, disrupting the coronary vasculature, or injecting drugs that may trigger arrhythmias or myocardial ischemia (e.g., epinephrine).

4.5.2 Electrocardiography

ECG analysis is a key component of advanced life support, serving both as a monitoring tool and as the basis for interventions such as drug therapy or defibrillation. Common initial arrest rhythms in veterinary patients include ventricular fibrillation, asystole, pulseless electrical activity, and sinus bradycardia.[15] The underlying rhythm often changes during the course of CPR, and this may dictate a change in therapy. Additionally, the cardiac rhythm often changes with the return of spontaneous circulation (ROSC), and this must be recognized and managed appropriately. Of intrest, and somewhat counterintuitive, ventricular fibrillation has the most specific therapy (defibrillation) and is considered the rhythm most responsive to treatment, but asystole was the most common initial arrest rhythm in a recent retrospective analysis of patients surviving CPR.[7]

Table 4-1 Guidelines for Drug Therapy and Initial Defibrillator Settings (Monophasic Waveform Defibrillators) During Cardiopulmonary Resuscitation

	Weight (lb)	**5**	**10**	**20**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**
	Weight (kg)	**2.5**	**5**	**10**	**15**	**20**	**25**	**30**	**35**	**40**	**45**	**50**
Drug (conc.)	**Dosage**	**ml or joules**										
Epi low (1:10,000)	0.01 mg/kg	0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Epi high (1:1000)	0.1 mg/kg	0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Atropine (0.54 mg/ml)	0.05 mg/kg	0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Lidocaine (20 mg/ml)	2 mg/kg	0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Sodium bicarbonate (1 mEq/ml)	1 mEq/kg	2.5	5	10	15	20	25	30	35	40	45	50
Calcium gluconate (100 mg/ml)	50 mg/kg	1	2.5	5	7.5	10	12.5	15	17.5	20	22.5	25
Magnesium sulfate (4 mEq/ml)	0.2 mEq/kg	0.1	0.25	0.5	0.75	1	1.25	1.5	1.75	2	2.25	2.5
Vasopressin (20 U/ml)	0.8 μ/kg	0.1	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.8	2
Amiodarone (50 mg/ml)	5 mg/kg	0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Naloxone (0.4 mg/ml)	0.04 mg/kg	0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Flumazenil (0.1 mg/ml)	0.02 mg/kg	0.5	1	2	3	4	5	6	7	8	9	10
External defibrillation	2-10 J/kg	20	30	50	100	200	200	200	300	300	300	360
Internal defibrillation	0.2-1 J/kg	2	3	5	10	20	20	20	30	30	30	50

Modified from Cole SG, Otto CM, Hughes D: Cardiopulmonary cerebral resuscitation in small animals: a clinical practice review. Part II, *J Vet Emerg Crit Care* 13:13, 2003.

4.5.3 Drug Therapy

Drug therapy during CPR is designed to augment basic life support techniques, enhancing blood flow to the myocardial and cerebral circulation, as well as to address factors that may have precipitated or will perpetuate cardiopulmonary arrest. Commonly used CPR drugs with dosage recommendations are shown in Table 4-1. Most drugs used in CPR may be given by several routes, with intravenous administration preferred (central venous administration is ideal). Other routes, including intraosseous or intratracheal, may also be used, but some medications, including sodium bicarbonate and calcium, are not recommended for intratracheal administration.

4.5.3.1 Fluid Therapy

Routine use of bolus IV fluid therapy during CPR is controversial. Fluid boluses are indicated in hypovolemic animals to restore blood volume and to maximize the cardiac output generated by compressions (see Chapter 65, Shock Fluids and Fluid Challenge). Additionally, rapidly administered fluids may be used to flush drugs and reduce transit time from the peripheral to central circulation. However, when an animal is euvolemic or hypervolemic, as may be the case when a hospitalized patient suffers cardiopulmonary arrest, bolus fluid therapy may cause a significant rise in central venous and, therefore, right atrial pressure. By increasing right atrial pressure, myocardial perfusion pressure is diminished, with potentially detrimental results. Thus the use of intravenous fluids during CPR should be determined on a case-by-case basis. 18

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4.5.3.2 Vagolytic Agents

Atropine is a vagolytic drug that abolishes parasympathetic tone and is indicated in patients that have cardiopulmonary arrest associated with slow pulseless electrical activity or asystole. Atropine is also indicated in patients with symptomatic bradycardia and in vagal arrests that may be experienced by debilitated patients with elevated vagal tone secondary to coughing, retching, vomiting, defecating, or to gastrointestinal, pulmonary, or neurologic disease. The dosage of atropine is 0.04 mg/kg IV, IT, or IO as necessary. Atropine is available in a 0.54 mg/ml concentration, and a shortcut dosage in an arrest situation is 1 ml/10 kg. It should be noted that the full-arrest dosage of atropine may produce a significant tachycardia in animals with perfusing rhythms. In this situation, it is recommended that the dosage be reduced to one fourth or half of the arrest dosage. Atropine may be repeated at 5-minute intervals as necessary during the course of CPR.

4.5.3.3 Vasopressors

Vasopressor drugs are used to increase vascular resistance and to increase aortic blood pressure during CPR (see Chapter 176, Vasoactive Catecholamines). This, in turn, maximizes myocardial and cerebral perfusion pressures and blood flow to the heart and brain. Vasopressors, such as epinephrine or vasopressin, are indicated in all types of cardiopulmonary arrest. Epinephrine is a catecholamine that has both strong α-adrenergic (vasopressor) and β-adrenergic (inotropic and chronotropic) effects. Studies have shown that the α-adrenergic effects are most important in CPR, and that the β-adrenergic effects may actually be detrimental to long-term outcome.[16,17] Epinephrine has both low-dosage and high-dosage recommendations, with the low dosage being 0.01 to 0.02 mg/kg and the high dosage being 0.1 to 0.2 mg/kg. Because the high dosage has been associated with worse neurologic outcomes in people (despite higher initial rates of ROSC), the low dosage is currently recommended in human CPR guidelines.[1] However, experimental evidence indicates that high-dosage epinephrine may be more effective than low-dosage epinephrine in dogs.[18] Epinephrine is available in a 1:1000 (1 mg/ml) concentration, and a shortcut for high-dosage (0.1 mg/kg) epinephrine is 1 ml/10 kg. Epinephrine may be given intravenously, intraosseously, or intratracheally and may be repeated at 5-minute intervals during CPR.

Vasopressin is a noncatecholamine vasopressor that is also included in CPR guidelines (see Chapter 177, Vasopressin).[1,3] It has a longer half-life than epinephrine and, unlike catecholamines, is effective in the presence of acidosis. Vasopressin also lacks potentially harmful β-adrenergic effects. The dosage of vasopressin is 0.8 unit/kg. Vasopressin may be given intravenously, intraosseously, or intratracheally and may be repeated at 5-minute intervals during CPR.

4.5.3.4 Antiarrhythmic Agents

Antiarrhythmic medication administration during CPR is limited to patients with either ventricular fibrillation or pulseless ventricular tachycardia that is not responsive to initial defibrillation (see Chapter 190, Antidysrhythmic Agents). Agents indicated in these cases include lidocaine and amiodarone. Lidocaine is a Class Ib antiarrhythmic agent that is administered at a dosage of 2 mg/kg IV, IO, or IT. Lidocaine is commonly available in a 2% (20 mg/ml) solution, and a shortcut dosage is 1 ml/10 kg. Some preparations of lidocaine that are used for local anesthesia contain preservatives, and preservative-free products are recommended for intravenous use. It should also be noted that lidocaine may suppress ventricular escape rhythms and, because of this, it should be used with caution following ROSC.

Amiodarone is a Class III antiarrhythmic drug that has recently been included in the human CPR guidelines.[1] There is limited experience with amiodarone in veterinary CPR; however, the dosage is 5 to 10 mg/kg IV. Amiodarone must be diluted, and hypotension during administration is a common occurrence.

4.5.3.5 Buffer Therapy

Although not routinely recommended in all patients, sodium bicarbonate is indicated in animals with preexisting acidosis, or in prolonged arrests lasting longer than 10 minutes. Because alkalinization shifts potassium into the intracellular compartment, sodium bicarbonate is also indicated in patients with severe hyperkalemia. The dosage for sodium bicarbonate is 1 to 2 mEq/kg IV or IO. Sodium bicarbonate inactivates surfactant, so it should not be given via the intratracheal route. Sodium bicarbonate typically is found as a 1 mEq/ml solution, and a shortcut dosage is 1 ml/kg.

4.5.3.6 Electrolyte Therapy

Calcium administration is not routinely recommended in CPR, because excess calcium may exacerbate ischemia-reperfusion injury. However, calcium gluconate is recommended in patients with severe hyperkalemia and in patients with known hypocalcemia. The dosage is 50 to 100 mg/kg IV or IO.

Magnesium sulfate is recommended in patients with known hypomagnesemia. Magnesium sulfate is also recommended with torsades de pointes, a rare form of polymorphic ventricular tachycardia that is extremely uncommon in veterinary patients. The dosage of magnesium sulfate is 30 mg/kg IV or IO.

4.5.4 Defibrillation

Electrical defibrillation is the only effective method to restore spontaneous circulation in a patient with ventricular fibrillation and is also indicated in patients with pulseless ventricular tachycardia. A more detailed discussion about the techniques and safety concerns regarding defibrillation may be found elsewhere in this text (see Chapter 53, Cardioversion and Defibrillation). In general, the following sequence for performing defibrillation is recommended.

First, the ECG rhythm of ventricular fibrillation or pulseless ventricular tachycardia is verified. Second, proper placement of the paddles is confirmed. Third, the operator announces the intention to defibrillate the patient, halts ongoing CPR, and calls, “Clear.” Fourth, following the call of “Clear,” the operator visually confirms that no personnel are in contact with the patient or table. Finally, firm pressure is applied with the paddle and the countershock is delivered.

The ECG is then monitored for the efficacy of the countershock and the patient is immediately reassessed for the return of spontaneous circulation. An energy setting of 2 to 10 joules/kg is selected for the initial external defibrillation attempt (or 0.2 to 1.0 joule/kg for internal defibrillation, see Box 4-1), with an increase in energy of approximately 50% for each subsequent attempt. 19

4.5.5 Anesthesia-Related Arrests

Anesthesia-related arrests are rare occurrences in most veterinary hospitals. However, because these arrests generally are recognized immediately and often have reversible causes, successful resuscitation is common. Anesthetic-related arrests should first be managed by turning off gas anesthesia and flushing the circuit with oxygen, or by discontinuing injectable drugs and administering reversal agents as indicated (e.g., flumazenil 0.02 to 0.04 mg/kg for benzodiazepines, naloxone 0.02 to 0.04 mg/kg for opioids, and yohimbine 0.1 mg/kg or atipamezole [equal volume to that of agonist] for α_2-agonists, xylazine and medetomidine, respectively). CPR should be instituted immediately. Open-chest CPR should be performed in patients undergoing thoracotomy and considered in patients undergoing celiotomy (via transdiaphragmatic access). Finally, an aggressive search for underlying causes of the arrest, such as hemorrhage, hypotension, hypoventilation, hypoxemia, or arrhythmias, should be conducted with immediate correction of identified problems.

4.6 MONITORING DURING CARDIOPULMONARY RESUSCITATION

Several methods of patient monitoring are available during CPR. Palpation of femoral pulses is one of the easiest parameters to monitor. Although the presence of pulses is often an encouraging finding, it should be noted that it is the pulse pressure, and not the blood pressure, that determines the pulse. Thus the ability to feel a pulse does not necessarily equate to adequate arterial blood pressure or perfusion. Conversely, $ETCO_2$ monitoring does provide a marker of blood flow during CPR. If ventilation remains constant, the $ETCO_2$ value is directly correlated to pulmonary perfusion and cardiac output during CPR, with higher $ETCO_2$ associated with increased myocardial perfusion pressure and increased rates of successful resuscitation.[19] Additionally, a large increase in the $ETCO_2$ level during CPR is often an indication of ROSC. $ETCO_2$ monitors are readily available and the technique is very easy to perform, making this an ideal monitoring tool during CPR.

ECG monitoring is essential during ongoing CPR, because changes in the underlying rhythm often dictate the type and timing of interventions. In some instances, such as with slow ventricular rhythms, the ECG tracing may represent either cardiopulmonary arrest or ROSC. Because of this, the ECG should be interpreted in conjunction with physical findings and other information (e.g., $ETCO_2$). If an apparent escape rhythm is present, audible heart sounds, palpable pulses, or markedly increased $ETCO_2$ should be present. If this is not the case, the rhythm represents pulseless electrical activity and CPR should be resumed.

Blood gas findings may be misleading during CPR. This is due to the large disparity between arterial and venous samples during low blood flow states. The arterial blood gas results may appear relatively normal, often demonstrating a respiratory alkalosis secondary to excessive ventilation in the face of diminished pulmonary blood flow. On the other hand, the venous blood gas indicates both respiratory and metabolic acidosis, and this is much more representative of the ischemia and decreased clearance of metabolic byproducts occurring in the local tissue environment.[20] Although this makes assessing the adequacy of ventilation from a venous sample impossible, overall the venous blood gas is a more useful monitoring tool during CPR.

4.7 POSTRESUSCITATION CARE

The care of a patient following ROSC is often as important to long-term survival as CPR itself. The likelihood of recurrent arrest is extremely high, especially if a reversible cause of the arrest is not identified and aggressively managed. Additionally, many postresuscitation syndromes occur secondary to the low blood flow and subsequent ischemia-reperfusion injury that occurs following circulatory arrest and CPR.[21,22] These syndromes include cardiovascular instability characterized by arrhythmias, myocardial dysfunction, and hypotension secondary to loss of vasomotor tone and is a common problem. Acute renal failure or compromise of the gastrointestinal mucosal barrier (so-called shock gut) secondary to hypoperfusion may also occur. Systemic inflammatory response syndrome may develop, with associated pulmonary involvement (acute lung injury [ALI] or acute respiratory distress syndrome [ARDS]), dysregulation of coagulation, and subsequent multiorgan dysfunction. Transient cerebral dysfunction is also very common after protracted cardiopulmonary arrest, although permanent neurologic abnormalities are rare in veterinary patients that survive to hospital discharge.[7] Finally, iatrogenic injury, including incisions for vascular access or thoracotomy, as well as rib fractures from external chest compressions, may also be present following CPR.

Intensive monitoring and aggressive therapy are generally necessary to optimize outcomes. Cardiac output, arterial blood pressure, and systemic oxygen transport should be maintained with fluid therapy, vasopressor or inotropic support, oxygen administration, and blood transfusion as necessary. Cerebral protection is also indicated and includes mannitol administration, head elevation, maintenance of normal blood pressure and oxygen delivery, as well as ensuring normocapnia. Many patients hypoventilate following an episode of cardiopulmonary arrest, so mechanical ventilation is often necessary following ROSC. It should be stressed that although hypercapnia should be avoided due to cerebral vasodilation and increases in intracranial pressure, hypocapnia should also be avoided, because hyperventilation may cause excessive vasoconstriction and decreased cerebral blood flow. Intentional induction of hypothermia (so-called protective hypothermia) is advocated in humans following CPR to minimize cerebral injury.[23] This has not yet translated into clinical veterinary practice; however, it is recommended that mildly hypothermic patients (>97° F) should not be aggressively rewarmed. As the postresuscitation period progresses, the timing of surgical intervention for either primary conditions underlying the arrest or for iatrogenic injury should be determined on a case-by-case basis. In many instances, it is useful to stage procedures to minimize the likelihood of recurrent arrest.

4.8 SUGGESTED FURTHER READING*

SG Cole, CM Otto, D Hughes: Cardiopulmonary cerebral resuscitation in small animals: a clinical practice review. Part I. *J Vet Emerg Crit Care*. **12**, 2002, 261, *Part I of a review of cardiopulmonary cerebral resuscitation in small animal patients containing guidelines for veterinary CPCR*.

SG Cole, CM Otto, D Hughes: Cardiopulmonary cerebral resuscitation in small animals: a clinical practice review. Part II. *J Vet Emerg Crit Care*. **13**, 2003, 13, *Part II of a review of cardiopulmonary cerebral resuscitation in small animal patients containing guidelines for veterinary CPCR*. 20

21 KH Kass, SC Haskins: Survival following cardiopulmonary resuscitation in dogs and cats. *J Vet Emerg Crit Care*. **2**, 1992, 57, *A retrospective analysis investigating outcomes of veterinary patients receiving CPR*.

TL Lehman, AM Manning: Postarrest syndrome and the respiratory and cardiovascular systems in postarrest patients. *Compend Contin Educ Vet Pract*. **25**, 2003, 492, *Part I of a review of postresuscitation syndromes in veterinary patients*.

TL Lehman, AM Manning: Renal, central nervous, and gastrointestinal symptoms in postarrest patients. *Compend Contin Educ Vet Pract*. **25**, 2003, 504, *Part II of a review of postresuscitation syndromes in veterinary patients*.

JE Waldrop, EA Rozanski, ED Swanke, et al.: Causes of cardiopulmonary arrest, resuscitation management, and functional outcome in dogs and cats surviving cardiopulmonary arrest. *J Vet Emerg Crit Care*. **14**, 2004, 22, *A retrospective review of patients surviving cardiopulmonary arrest. The first study specifically evaluating the neurologic outcome of veterinary CPR survivors.*

* See the CD-ROM for a complete list of references

5 Chapter 5 Hyperthermia and Fever*

James B. Miller, DVM, MS, DACVIM

5.1 KEY POINTS

- Thermoregulation is controlled by a region of the hypothalamus. It responds to thermoreceptors in the brain and peripheral nervous system to maintain a narrow range of body temperature by increasing either heat production or loss.
- Hyperthermia describes any elevation in core body temperature above accepted normal values.
- A true fever is the body's normal response to infection between injury and is part of the acute phase response. It is controlled by the thermoregulatory center in the hypothalamus.
- Other forms of hyperthermia are a result of an imbalance between heat production and heat loss. Hyperthermic patients are approached differently from those with a fever, both diagnostically and therapeutically.
- A fever may be beneficial to the host by decreasing bacterial growth and inhibiting viral replication. Most fevers are not a threat to life unless body temperature exceeds 107° F (41.6° C).
- A fever will increase water and caloric requirements, and this must be considered when treating the febrile patient.
- In most cases, an accurate diagnosis should be obtained before initiating nonspecific therapy for a fever.
- Nonsteroidal antiinflammatory drugs will reduce a fever without blocking the rest of the acute phase response. Glucocorticoids will reduce a fever, but they also block the inflammatory reaction.
- Total body cooling may be counter-productive and usually is reserved for afebrile hyperthermia or when fevers approach 107° F.
- Antibiotics should not be used nonspecifically for fever management without a strong indication of infection that may be susceptible to their action.

* Modified from Miller JB: Hyperthermia and fever of unknown origin. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 6, St Louis, 2005, Saunders.

5.2 INTRODUCTION

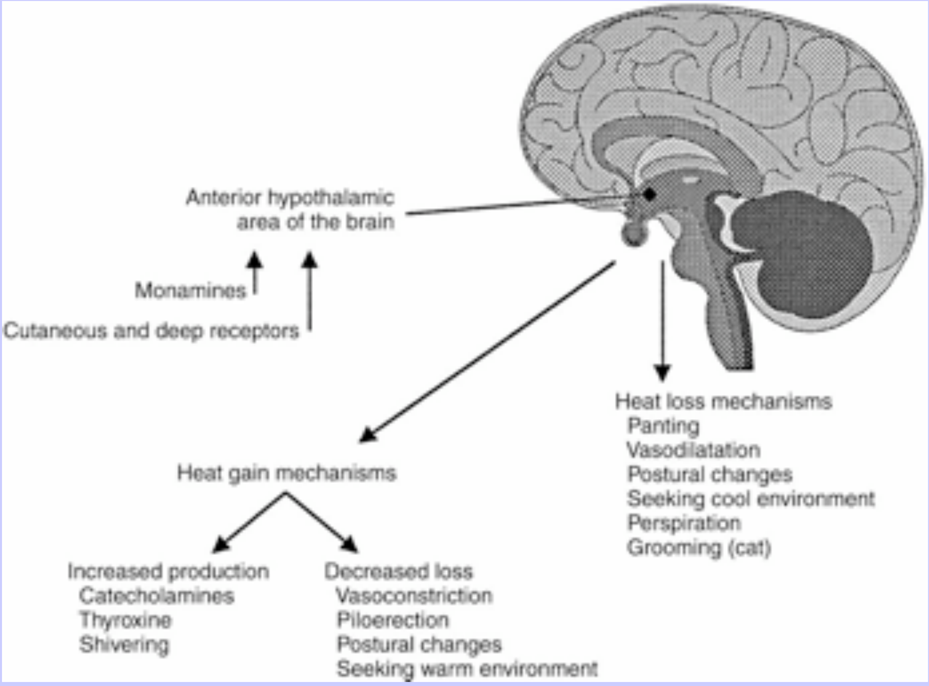
Obtaining a body temperature measurement is important in the evaluation of all patients, especially the critical care patient. A rectal temperature higher than 102.5° F is considered elevated in the unstressed dog or cat. The method of measurement must also be taken into account because ear, axillary, or toe web measurements will be lower than rectal temperatures. An intravascular thermistor is considered most accurate, but often impractical in the clinical setting.

Too frequently the veterinarian associates any elevation in body temperature with true fever. The assumption is often made that the fever is caused by an infectious agent, even if there is no obvious cause. If the patient's fever resolves after antibiotics are given, the assumption is made that it was caused by a bacterial infection. A normal body temperature is often assumed to indicate the absence of disease. This approach to fever, hyperthermia, or normothermia can be misleading and result in improper diagnoses and therapy (or the lack thereof).

5.3 THERMOREGULATION

Thermoregulation is the balance between heat loss and heat production. Metabolic, physiologic, and behavioral mecha-nisms are used by homeotherms to regulate heat loss and production. The thermoregulatory control center for the body is located in the central nervous system in the preoptic area of the anterior hypothalamus (AH).[1] Changes in ambient and core body temperatures are sensed by the peripheral and central thermoreceptors, and information is conveyed to the AH via the nervous system. The thermoreceptors sense that the body is below or above its normal temperature (set point) and subsequently cause the AH to stimulate the body to increase heat production and reduce heat loss through conservation if the body is too cold, or to dissipate heat if the body is too warm (Figure 5-1). Through these mechanisms, the dog and cat can maintain a narrow core body temperature range in a wide variety of environmental conditions and activity levels. With normal ambient temperatures, most body heat is produced by muscular activity, even while at rest. Cachectic or anesthetized patients or those with severe neurologic impairment may not be able to maintain a normal set point or generate a normal response to changes in core body temperature.

Figure 5-1 Schematic representation of normal thermoregulation. From Miller JB: Hyperthermia and fever of unknown origin. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 6, St Louis, 2005, Saunders.



5.4 HYPERTHERMIA

Hyperthermia is the term used to describe any elevation in core body temperature above the accepted normal range for that species. When heat is produced or stored in the body at a rate greater than it is lost, hyperthermia results.[2,11] The term *fever* is reserved for those hyperthermic animals in which the set point in the AH has been reset to a higher temperature. In hyperthermic states other than fever, temperature elevation is not a result of the body attempting to raise its temperature but is due to the physiologic, pathologic, or pharmacologic changes that cause heat gain to exceed heat loss. Box 5-1 outlines the various classifications of hyperthermia.

5.5 TRUE FEVER

True fever is a normal response of the body to invasion or injury and is part of the "acute phase response."[3] Other parts of the acute phase response include increased neutrophil numbers and phagocytic ability, enhanced T and B lymphocyte activity, increased acute phase protein production by the liver, increased fibroblast activity, and increased sleep. Fever and other parts of the acute phase response are initiated by exogenous pyrogens that lead to the release of endogenous pyrogens (Figure 5-2).[4]

5.5.1 Box 5-1 Classification of Hyperthermia

5.5.1.1 True Fever

Production of endogenous pyrogens

5.5.1.2 Inadequate Heat Dissipation

Heat stroke

Hyperpyrexic syndromes

5.5.1.3 Exercise-Induced Hyperthermia

Normal exercise

Hypocalcemic tetany (eclampsia)

Seizure disorders

5.5.1.4 Pathologic or Pharmacologic Origin

Lesions in or around the anterior hypothalamus

Malignant hyperthermia

Hypermetabolic disorders

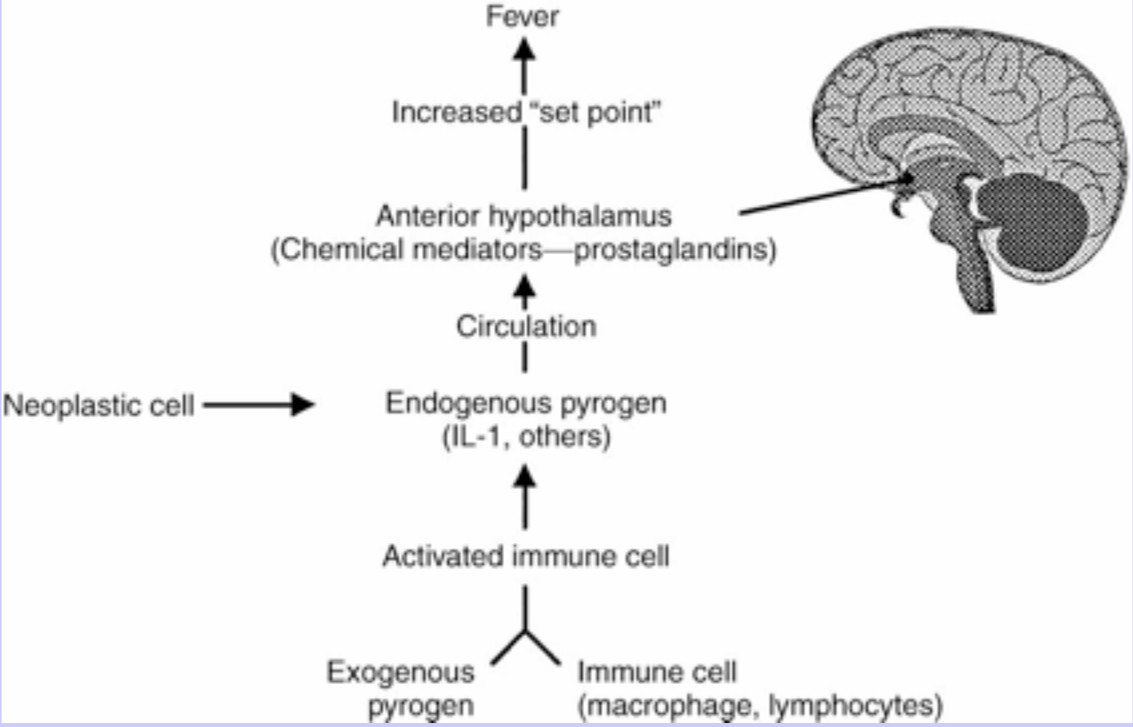
Monoamine metabolism disturbances

From Miller JB: Hyperthermia and fever of unknown origin. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 6, St Louis, 2005, Saunders.

5.5.2 Exogenous Pyrogens

True fever may be initiated by a variety of substances including infectious agents or their products, immune complexes, tissue inflammation or necrosis, and several pharmacologic agents. Collectively, these substances are called *exogenous pyrogens*. Their ability to directly affect the thermoregulatory center is probably minimal and they primarily cause the release of endogenous pyrogens by the host. Box 5-2 lists some of the more important known exogenous pyrogens.

Figure 5-2 Schematic representation of the pathophysiology of fever. From Miller JB: Hyperthermia and fever of unknown origin. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 6, St Louis, 2005, Saunders.



5.5.2.1 Box 5-2 Exogenous Pyrogens

5.5.2.1.1 Infectious Agents

5.5.2.1.1.1 Bacteria (Live and Killed)

- Gram positive
- Gram negative

5.5.2.1.1.2 Bacterial Products

- Lipopolysaccharides
- Streptococcal exotoxin
- Staphylococcal enterotoxin
- Staphylococcal proteins

5.5.2.1.1.3 Fungi (Live and Killed)

- Fungal products
- Cryptococcal polysaccharide
- Cryptococcal proteins

5.5.2.1.1.4 Viruses

5.5.2.1.1.4.1 Rickettsiae

5.5.2.1.1.4.1.1 Protozoa

5.5.2.1.1.4.1.1.1 Nonmicrobial Agents

5.5.2.1.1.4.1.1.1.1 Soluble Antigen-Antibody Complexes

5.5.2.1.1.4.1.1.1.1.1 Bile Acids

5.5.2.1.1.4.1.1.1.1.1.1 Pharmacologic Agents

Bleomycin

Colchicine

Tetracycline

Levamisole (cats)

Tissue Inflammation and Necrosis

From Miller JB: Hyperthermia and fever of unknown origin. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 6, St Louis, 2005, Saunders.

5.5.3 Endogenous Pyrogens

In response to stimulation by an exogenous pyrogen, proteins (cytokines) released from cells of the immune system trigger the febrile response. Macrophages are the primary immune cells involved, although T and B lymphocytes and other leukocytes may play significant roles. The proteins produced are called *endogenous pyrogens* or *fever-producing cytokines*. Although interleukin-1, interleukin-6, and tumor necrosis factor-α are considered the most important fever-producing cytokines, at least 11 cytokines are capable of initiating a febrile response (Table 5-1).

Some neoplastic cells are also capable of producing cytokines that lead to a febrile response. The cytokines travel via the bloodstream to the AH where they bind to the vascular endothelial cells within the AH and stimulate the release of prostaglandins (PGs), primarily PGE_2 and possibly $PGF_{2\alpha}$. The set point is raised and the core body temperature rises through increased heat production and conservation.

Table 5-1 Proteins With Pyrogenic Activity

Endogenous Pyrogen	**Principal Source**
Cachectin (TNF-α)	Macrophages
Lymphotoxin (TNF-β)	Lymphocytes (T and B)
IL-1α	Macrophages and many other cell types
IL-1β	
Interferon-α	Leukocytes (esp. monocyte-macrophages)
Interferon-β	Fibroblasts
Interferon-γ	T lymphocytes
IL-6	Many cell types
Macrophage inflammatory protein 1α	Macrophages
Macrophage inflammatory protein 1β	
IL-8	

From Miller JB: Hyperthermia and fever of unknown origin. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 6, St. Louis, 2005, Saunders. Adapted from Beutler B, Beutler SM: The pathogenesis of fever. In Bennett JC, Plum F, editors: *Cecil textbook of medicine*, ed 20, Philadelphia, 1996, Saunders.

IL, Interleukin; *TNF*, tumor necrosis factor;

5.6 INADEQUATE HEAT DISSIPATION

5.6.1 Heat Stroke

Heat stroke is a common result of inadequate heat dissipation (see Chapter 167, Heat Stroke). Exposure to high ambient temperatures may increase heat load at a faster rate than it can be dissipated from the body. This is 23 especially true 24 in larger breeds of dogs and obese or brachycephalic animals. Heat stroke may occur rapidly, especially in closed environments with poor ventilation (e.g., inside a car with the windows closed), even on only moderately hot days. Environmental temperatures inside a closed car exposed to direct sun may exceed 120° F (48° C) in less than 20 minutes, even when the outside temperature is only 75° F (24° C). Death may occur in less than an hour, especially in the predisposed animal types described above.

Heat stroke will not respond to antipyretics used for the management of a true fever. The severely hyperthermic patient must have total body cooling immediately to prevent organ damage or death. Mechanisms of heat loss from the body include the following: radiation (electromagnetic or heat exchange between objects in the environment), conduction (between the body and environmental objects that are in direct contact with the skin, as determined by the relative temperatures and gradients), convection (the movement of fluid, air, or water over the surface of the body), and evaporation (disruption of heat by the energy required to convert the material from a liquid to a gas, as with panting). There are numerous strategies for cooling the hyperthermic patient (Box 5-3), and the technique(s) chosen should be based on the severity of the animal's condition, temperature, and response to therapy.

In most veterinary patients, total body cooling is best accomplished by administering oxygen and intravenous fluid therapy (see Chapters 19 and 65, Oxygen Therapy and Shock Fluids and Fluid Challenge, respectively), water baths and rinses using tepid water, and placing a fan near the animal. If the water applied to the animal is too cold, there is a tendency for peripheral vasoconstriction that will inhibit radiant heat loss and slow the cooling process. Cooling should be discontinued when body temperature approaches normal (approximately 103° F or 39.4° C) to prevent iatrogenic hypothermia.

5.6.1.1 Box 5-3 Cooling Options for the Hyperthermic Patient

5.6.1.1.1 Oxygen and Intravenous Isotonic Fluid Therapy

5.6.1.1.1.1 Surface Cooling Techniques

- Clip fur if indicated
- Tepid water applied to skin or whole body (manually or via bath)
- Fan
- Ice packs over areas with large vessels (neck, axilla, inguinal region)
- Combination of the above

5.6.1.1.2 Internal Cooling Techniques

- Rectal administration of cool isotonic fluids
- Gastric lavage
- Open body cavity
- Peritoneal dialysis

5.6.1.1.3 Extracorporeal Techniques

5.6.1.1.3.1 Antipyretic Drugs

- Antiprostaglandins
- Dantrolene

Dipyrone

Aminopyrine

COX-2 inhibitors

Glucocorticoids

Additional NSAIDs

COX-2, Cyclooxygenase-2; *NSAIDs,* nonsteroidal antiinflammatory drugs.

5.6.2 Hyperpyrexic Syndrome

Hyperpyrexic syndrome is associated with moderate to severe exercise in hot and humid climates. This syndrome may be more common in hunting dogs or dogs that “jog” with their owners. In humid environments, evaporative cooling via panting is minimal. In addition, heavy exercise may cause the cardiovascular system to supply skeletal muscles with adequate blood flow while compromising peripheral heat loss by not enabling proper vasodilation in the skin.

Many hunting dogs and dogs that run with their owners will continue to work or run until they become weak, stagger, and collapse. In suspected cases of hyperpyrexic syndrome, owners should obtain a rectal thermometer and evaluate the dog's rectal temperature at the first sign that the dog is becoming weak or does not want to continue. Owners should be instructed that rectal temperatures above 106° F (41° C) require immediate total body cooling, and temperatures above 107° F (41.6° C) may lead to permanent organ damage or death.

5.6.3 Exercise-Induced Hyperthermia

The body temperature will rise with sustained exercise of even moderate intensity because of heat production associated with muscular activity. Even when extreme heat and humidity are not factors, the dog occasionally will reach temperatures that require total body cooling. This is especially true in dogs that do not exercise frequently, are overweight, or have respiratory disease.

Eclampsia results in extreme muscular activity that can lead to significant heat production and result in severe hyperthermia. Total body cooling should be initiated if the patient is hyperthermic, in conjunction with therapy for the eclampsia (see Chapters 56 and 140, Calcium Disorders and Dystocia and Obstetric Crises, respectively).

Seizure disorders due to organic, metabolic, or idiopathic causes are encountered frequently in small animals (see Chapter 98, Seizures and Status Epilepticus). Hyperthermia associated with severe muscular activity can result, especially if the seizures are prolonged or occur in clusters. The initial concern of the clinician should be to stop the seizures, but when significant hyperthermia is present, total body cooling is also recommended.

5.6.4 Pathologic and Pharmacologic Hyperthermia

The pathologic and pharmacologic types of hyperthermia encompass several disorders that will impair the heat balance equation. Hypothalamic lesions may obliterate the thermoregulatory center, leading to impaired responses to both hot and cold environments. Malignant hyperthermia (MH) has been reported in the dog and cat. It leads to a myopathy and subsequent metabolic heat production, secondary to disturbed calcium metabolism that is initiated by pharmacologic agents such as inhalation anesthetics (especially halothane) and muscle relaxants such as succinylcholine. Extreme muscle rigidity may or may not be present. Removal of the offending causative agent and total body cooling may prevent death. Dantrolene is a specific and effective therapy for malignant hyperthermia and is dosed at 2.5 to 5 mg/kg IV.

Hypermetabolic disorders may also lead to hyperthermic states. Endocrine disorders such as hyperthyroidism and pheochromocytoma can lead to an increased metabolic rate or vasoconstriction, resulting in excess heat production and/or decreased ability to dissipate heat, or both. These conditions rarely lead to severe hyperthermia that requires total body cooling.

5.7 BENEFITS AND DETRIMENTS OF HYPERTHERMIA

5.7.1 Benefits

Fever is part of the acute phase response and is a normal response of the body. Even poikilotherms such as fish and reptiles will respond to a pyrogen by seeking higher environmental temperatures to raise their body temperatures.[5] It would be logical to think that a true fever is beneficial to the host. Most studies have shown that a fever will reduce the duration of morbidity and mortality from many infectious diseases. A fever decreases the ability of many bacteria to use iron, which is necessary for them to live and replicate.[5] Blocking the fever with nonsteroidal antiinflammatory drugs (NSAIDs) in rabbits with *Pasteurella* infections significantly increases mortality rates. Many viruses are heat sensitive and cannot replicate in high temperatures. Raising the body temperature in neonatal dogs with herpesvirus infections significantly reduces the mortality rate.

5.7.2 Detriments

Hyperthermia leads to an increased metabolic state and level of oxygen consumption that raise both caloric and water requirements by approximately 7% for each degree Fahrenheit (0.6° C) above accepted normal values. In addition, hyperthermia leads to suppression of the appetite center in the hypothalamus but usually not the thirst center. Animals that have sustained head trauma or a cerebrovascular accident may suffer more severe brain damage if coexisting hyperthermia is present.

Body temperatures above 107° F (41.6° C) often lead to increases in cellular oxygen consumption that exceed oxygen delivery, resulting in deterioration of cellular function and integrity. This may lead to disseminated intravascular coagulation (DIC) (see Chapter 117, Hypercoagulable States) with thrombosis and bleeding, or serious damage to organ systems including the brain (cerebral edema and subsequent confusion, delirium, obtundation, seizures, coma), heart (arrhythmias), liver (hypoglycemia, hyperbilirubinemia), gastrointestinal tract (epithelial desquamation, endotoxin absorption, bleeding), and kidneys (acute renal failure; see Chapter 167, Heat Stroke). Additional abnormalities might include hypoxemia, hyperkalemia, skeletal muscle cytolysis, tachypnea, metabolic acidosis, tachycardia, tachypnea, and hyperventilation.

Exertional heat stroke and malignant hyperthermia may lead to severe rhabdomyolysis, hyperkalemia, hypocalcemia, myoglobinemia and myoglobinuria, and elevated levels of creatine phosphokinase. Fortunately, true fevers rarely lead to body temperatures of this magnitude and are usually a result of other causes of hyperthermia that should be managed as medical emergencies.

5.8 CLINICAL APPROACH TO THE HYPERTHERMIC PATIENT

In evaluating presented with a hyperthermic patient, the problem should be approached in a logical manner to avoid making erroneous conclusions.[2] A complete history and physical examination should be performed unless the patient is critically ill or severely hyperthermic (temperature higher than 106° F) and the patient is obviously attempting to dissipate heat (panting, postural changes) or is comatose. In such cases, immediate total body cooling and supportive care should be initiated.

In stable patients, a thorough physical examination and specific questions concerning previous injuries or infections, exposure to other animals, disease in other household pets, previous geographic environment, and previous or current drug therapy are beneficial. This approach enables the clinician to decide if the elevated body temperature is a true fever. Temperatures less than 106° F (41° C), unless prolonged, are usually not life threatening, and caution should be taken when administering antipyretic therapy is considered before performing a proper clinical evaluation.

5.9 NONSPECIFIC THERAPY FOR FEBRILE PATIENTS

Mild to moderate elevations in body temperature are rarely fatal and may be beneficial to the body. As stated before, hyperthermia may inhibit viral replication, increase leukocyte function, and decrease the uptake of iron by microbes (which is often necessary for their growth and replication). If a fever exceeds 107° F, a significant risk of permanent organ damage and DIC exists. The benefits of nonspecific therapy versus its potential negative effects should be considered before initiating such management.

Nonspecific therapy for true fever usually involves inhibitors of prostaglandin synthesis. The compounds most commonly used are the NSAIDs. These products inhibit the chemical mediators of fever production and allow normal thermoregulation. They do not block the production of endogenous pyrogens.[2] These products are relatively safe, although acetylsalicylic acid is potentially very toxic to the cat (cyclooxygenase-2 [COX-2] inhibitors are relatively safe) and animals with gastrointestinal ulceration or renal disease should not receive these drugs. Dipyrone, an injectable nonsteroidal antiinflammatory drug sometimes used in cats, may lead to bone marrow suppression, especially when given over a prolonged period.

Total body cooling with water, fans, or both, in a febrile patient will reduce body temperature; however, the thermoregulatory center in the hypothalamus will still be directing the body to increase the body temperature. This may result in a further increase in metabolic rate, oxygen consumption, and subsequent water and caloric requirements. Unless a fever is life threatening, this type of nonspecific therapy is counterproductive.

Glucocorticoids block the acute phase response, fever, and most other parts of this (adaptive) response. In general, their use should be reserved for those patients in whom the cause of the fever is known to be noninfectious and blocking the rest of the acute phase response will not be detrimental (and may prove beneficial). The most common indications include some immune-mediated diseases in which fever plays a significant role and glucocorticoid therapy is often part of the chemotherapeutic protocol (e.g., immune-mediated hemolytic anemia, immune-mediated polyarthritis).

Phenothiazines can be effective in alleviating a true fever by depressing normal thermoregulation and causing peripheral vasodilation. The sedative qualities of the phenothiazines and their potential for hypotension caused by the phenothiazines should be considered before administration to the febrile patient.

5.10 THE FEBRILE INTENSIVE CARE PATIENT

Fever is a common problem in critically ill veterinary patients. The clinician must attempt to exclude noninfectious causes and then determine the infection site and likely pathogens in those with infections. Intensive care patients frequently have both infectious and noninfectious causes of fever, which necessitates a systematic and comprehensive diagnostic approach. Altered immune function, indwelling catheter devices, and more invasive monitoring and treatment approaches put these patients at high risk for inflammation and infection.

Noninfectious causes of fever in intensive care patients commonly include phlebitis or thrombophlebitis, postoperative inflammation, posttransfusion reactions, pancreatitis, hepatitis, cholecystitis, aspiration pneumonitis, acute respiratory distress syndrome, and neoplastic processes.

Nosocomial infection in critically ill patients is an important cause of new-onset fevers. Although incidence studies have not been performed in veterinary patients, the reported range in people is 3% to 31%. Commonly implicated sources include the lungs (aspiration or ventilator-associated pneumonia), bloodstream, catheters, incisions, and the urinary tract. An initial diagnostic evaluation might include a complete blood count, thoracic and abdominal imaging, and close inspection of all catheter sites or incisions. Additional diagnostic tests that might be indicated include culture and sensitivity testing of blood, urine, airway fluid, pleural or peritoneal effusions, postoperative incisions, cerebrospinal fluid, joint fluid, nasal discharge, and/or diarrhea.

Antibiotics are indicated for the febrile patient only when a specific pathogen is known or strongly suspected.[2] The use of antibiotics in these patients without knowledge that a microbial agent is causing the fever can lead to bacterial resistance (see Chapter 194, Antimicrobial Use in the Critical Care Patient). If there is no obvious source of infection and the patient is not deteriorating or neutropenic, antibiotic additions or changes should be delayed until more definitive information is obtained.

5.11 SUGGESTED FURTHER READING*

MT Berlin, AM Abeche: Evolutionary approach to medicine. *South Med J*. **94**, 2001, 26, An excellent article about the febrile response in many species, with discussion of the benefits of fever. Very well referenced.

B Beutler, SM Buetler: The pathogenesis of fever. In JC Bennet, F Plum (Eds.): *Cecil textbook of medicine*. ed 20, 1996, Saunders, Philadelphia, A review of the pathophysiology of the febrile response. A short chapter that discusses the various exogenous and endogenous pyrogens.

JG Cunningham: In *Textbook of veterinary physiology*. ed 2, 1997, Saunders, Philadelphia, A short review of the normal thermal regulation system in the body.

CA Dinarella: The acute phase response. In JC Bennet, F Plum (Eds.): *Cecil textbook of medicine*. ed 20, 1996, Saunders, Philadelphia, A short discussion of the acute phase response and its potential benefits to the body.

PA Mackowiac: Approach to the febrile patient. In HD Humes (Ed.): *Kelley's textbook of internal medicine*. ed 4, 2000, Lippincott Williams & Wilkins, Philadelphia, An approach to the human patient with fever. Many similarities to the animal patient with many of the same concerns on use of antipyretics and antibiotics.

* See the CD-ROM for a complete list of references.

6 Chapter 6 Hypotension

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6.1 Key Points

- Blood pressure is a combination of the effects of various elements. These include heart rate, stroke volume, and systemic vascular resistance.
- Hypotension occurs when at least one of the controls of blood pressure is overcome or neutralized.
- Treatment of hypotension involves treating the underlying cause and targeting the patient's normal control mechanisms.

6.2 INTRODUCTION

Hypotension, or low arterial blood pressure, is not a disease. Instead, hypotension is a clinical manifestation of many different diseases. Although a wide variety of diseases can cause hypotension, it results from a failure of common regulatory mechanisms. Understanding these mechanisms helps to guide the diagnosis and treatment of hypotensive disorders.

6.3 COMPONENTS OF BLOOD PRESSURE

6.3.1 Physiology of Blood Pressure

Blood pressure is the force that the flow of blood puts on the walls of the vessels. The three measurements of arterial blood pressure are systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP). SAP and DAP measurements correspond to the respective phase of the cardiac cycle. MAP equates to overall pressure throughout the cardiac cycle. Because most of the cardiac cycle is spent in diastole, so too most of the mean blood pressure is affected by the diastolic blood pressure. This can be demonstrated by one of the formulas used to calculate MAP: $\text{MAP} = ([\text{SAP} - \text{DAP}] \div 3) + \text{DAP}$. When considering the perfusion pressure of organs, the MAP is more important than either SAP or DAP.[1,2] However, coronary perfusion occurs during diastole.

The cardiovascular determinants of blood pressure are cardiac output and systemic vascular resistance (SVR). Therefore blood pressure can be represented by the following formula:

$$\text{BP} = \text{CO} \times \text{SVR}$$

where *BP* is blood pressure, *CO* is cardiac output, and *SVR* is systemic vascular resistance. *Cardiac output* is the product of the heart rate and the stroke volume ($\text{CO} = \text{HR} \times \text{SV}$). *Stroke volume* is the amount of blood ejected with each heartbeat and is affected by the preload, contractility, and afterload.[1] *Vascular resistance* refers to the effects of vascular tone and blood viscosity on flow through a blood vessel. Resistance to blood flow through a vessel increases as the blood becomes more viscous and as the vessel becomes more constricted. Thus hypotension is typically the result of a decrease in the heart rate, stroke volume, the systolic vascular resistance of the entire arterial vasculature, or, more commonly, a combination.[2]

6.3.2 Pathophysiology of Blood Pressure

Within physiologic limits, neural, hormonal, and local metabolites regulate the control of systemic blood pressure. All blood vessels containing smooth muscle are innervated by fibers of the sympathetic arm of the autonomic nervous system. Sympathetic fibers innervating resistance vessels are noradrenergic and vasoconstricting in function, except in the skeletal muscle, where sympathetic fibers are cholinergic and vasodilatory. Noradrenergic fibers course through the adventitia of arterioles and release the neurotransmitter norepinephrine in a persistent or tonic fashion. Intracellular events following receptor binding of norepinephrine result in contraction of the smooth muscle. Constriction of resistance vessels is mediated by an increase in the frequency of sympathetic noradrenergic release of norepinephrine. In contrast, vasodilation results from a decrease in the rate of tonic sympathetic discharge of norepinephrine.[1-3]

Sympathetic noradrenergic innervation of cardiac muscle mediates increases in heart rate (chronotropic effect) and force of contraction (inotropic effect). Cholinergic fibers carried in the vagus nerve mediate a decrease in heart rate and oppose the chronotropic effects of sympathetic discharge. Both sympathetic and vagal fibers discharge in a tonic fashion, although vagal tonic discharge predominates at rest.[1,2]

The rate of tonic sympathetic discharge is controlled by a group of neurons in the medulla oblongata called the *vasomotor center*. Vasomotor center neurons activate sympathetic preganglionic neurons on the intermediolateral gray matter of the spinal cord. These fibers leave the spinal cord and converge at sympathetic ganglia. Postganglionic nerves arise from the sympathetic ganglia and terminate in the adventitia of blood vessels. Stimulation of vasomotor center neurons occurs directly during hypoxia and hypercapnia. The resultant increase in sympathetic tonic discharge leads to a rise in systemic blood pressure.

The vasomotor center receives afferent fibers from arterial and venous baroreceptors and from carotid and aortic chemoreceptors. Baroreceptors are stretch receptors located in the left atrium, aortic arch, and carotid sinus. Upon distention or increased pressure in these structures, baroreceptor discharges are increased, leading to inhibition of the sympathetic nervous system and activation of the parasympathetic nervous system. This results in vasodilation, bradycardia, and a decrease in contractility in an attempt to decrease MAP. Conversely, when hypotension is present, the rate of baroreceptor discharge decreases, and this minimizes the inhibitory (vasodilatory) influence on the vasomotor center results in activation of the sympathetic nervous system and inhibition of the parasympathetic nervous system. This feedback system controls arterial blood pressure within physiologic limits of approximately 50 mm Hg and 150 mm Hg.[3] Beyond these limits, the rate of baroreceptor discharge has been maximized or minimized, respectively, and cannot cause a further change in blood pressure. 27 28

Local hypoxia or hypercarbia (acidosis) resulting from arterial hypotension stimulates chemoreceptors in the carotid sinus and aortic bodies. Afferent fibers from the chemoreceptors stimulate the vasomotor center and result in vasopressor and tachycardic responses. The chemoreceptor feedback system is less important than the baroreceptor reflex for acute changes in blood pressure.[4,5]

Stretch receptors in the atria and pulmonary artery respond to distention of the venous system. Stimulation of these stretch receptors results in inhibition of the vasomotor center, vasodilation, and a decrease in blood pressure. Similar to what occurs with the baroreceptors of the arterial system, the absence of venous distention and increased atrial filling pressure removes this inhibitory influence on the vasomotor center.

Circulating hormones released during inflammation have vasodilating properties on resistance vessels.[5,6] Adrenal medullary norepinephrine and epinephrine, vasopressin, and angiotensin II are examples of circulating hormones that have vasoconstricting properties on vascular smooth muscle. Metabolites derived from endothelial cells, inflammatory cells, and platelets exert a paracrine effect on vasomotor tone and can influence systemic blood pressure. Prostacyclin is a metabolite of arachidonic acid produced by endothelial cells. Prostacyclin inhibits platelet aggregation and causes vasodilation. Nitric oxide (NO) is a gaseous molecule derived from arginine within endothelial cells. There is a tonic production and release of NO in the presence of the calmodulin-dependent enzyme NO synthase in the cell membrane. This constitutive synthesis by NO synthase is in contrast to inducible production of NO by inducible NO synthase located in the cytosol. Inducible nitric oxide production occurs in response to inflammatory stimulation. Both forms of NO cause vascular smooth muscle relaxation by activating guanylyl cyclase. Various cytokines (interleukin [IL]-1B, IL-2, IL-6, tumor necrosis factor, and interferon-γ) and lipopolysaccharide derived from the cell membrane of gram-negative bacteria are also potent inducers of cytosolic NO synthase.[6,7]

Thromboxane A_2 and endothelins are metabolites that cause vasoconstriction of vascular smooth muscle. Thromboxane A_2 is synthesized from arachidonic acid in the presence of phospholipid A_2 by platelets. In addition to facilitating platelet aggregation, thromboxane A_2 is a vasoconstricting agent. Endothelins are a group of vasoconstricting polypeptides produced by endothelial cells. When administered intravascularly in experimental animals, endothelins produce an initial fall in blood pressure followed by a prolonged pressor response. Endothelins also have positive inotropic and chronotropic properties.

The baroreceptor-mediated increase in sympathetic output is the initial and most important physiologic response to hypotension. Although adrenal medullary secretion of catecholamines is increased, it is the local release of norepinephrine by postganglionic nerve fibers at the arteriolar level that is responsible for the generalized vasoconstrictor response. Vasoconstriction is greatest in the skin, kidneys, and viscera, shunting blood to the systemic circulation. The brain and heart experience vasodilation in an attempt to maximize blood flow to these vital organs. Increased circulating levels of angiotensin II, aldosterone, and vasopressin also assist the pressor response by direct vasoconstriction or expansion of intravascular volume (see Chapter 177, Vasopressin).

In refractory shock, hypotension persists despite physiologic compensation and an adequate intravascular fluid volume. Vascular spasm or extreme vasodilation of precapillary arterioles, blunting of vasomotor function due to prolonged cerebral ischemia, increased capillary permeability and fluid loss, and myocardial dysfunction result from persistent tissue hypoxia. Distributive (or vasogenic) shock, a common result of diseases such as sepsis or anaphylaxis, is associated with extreme vasodilation of some vascular beds and vasoconstriction in other tissues. Vasoplegia is the lack of responsiveness of blood vessels to physiologic regulatory mechanisms. Overproduction of NO, depletion of endogenous vasopressin, downregulation of catecholamine receptors, and disruption of vascular smooth muscle calcium metabolism are thought to be responsible for vasoplegia and refractory shock.

Cardiogenic causes for hypotension may also occur. This can occur with either primary or secondary cardiac diseases.[1,3] Primary cardiac diseases occur when the pathologic process originates within the heart, as seen in dilated cardiomyopathy or third-degree atrioventricular block. Secondary cardiac diseases occur when pathology originates outside the heart, but either suppresses normal heart function or causes secondary sites of pathology in the heart. Diseases that induce systemic inflammatory response syndrome, for instance, may cause the release of cardiac suppressing factors or decrease the heart's response to sympathetic nervous system stimulation.[4]

6.4 MEASURING BLOOD PRESSURE

6.4.1 Normal Values

Because MAP is most closely related to the overall perfusion pressure, hypotension is best identified as an abnormally low MAP, typically defined as less than 60 mm Hg (Table 6-1). At this pressure, the ability of the kidney to maintain glomerular filtration rate is impaired and cerebral perfusion may be compromised. Because there is no exact correlation of systolic or diastolic pressure to MAP, these values should be used cautiously and are not as consistent in peripheral vessels. Thus blood pressure in the aorta can be approximated by femoral or dorsal pedal arterial blood pressure, but much greater variation occurs with systolic and diastolic blood pressures (see Chapter 203, Hemodynamic Monitoring).

Table 6-1 Normal Arterial Blood Pressure Values in Dogs and Cats

	Dogs	Cats
Systolic arterial pressure	90 to 140 mm Hg	80 to 140 mm Hg
Diastolic arterial pressure	50 to 80 mm Hg	55 to 75 mm Hg
Mean arterial pressure	60 to 100 mm Hg	60 to 100 mm Hg

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29

6.4.2 Direct Measurement

Blood pressure can be measured either directly or indirectly, but direct measurement is more accurate. To measure directly, a catheter must be placed in an artery (most commonly the dorsopedal or femoral artery) and connected to a pressure transducer that allows for continuous measurement and reading of SAP, DAP, and MAP. In addition, the catheter may be used for arterial blood sampling and analysis.

The disadvantages of this method are the increased technical difficulty, invasiveness, cost of the equipment, and the risk of thrombosis, bleeding, inflammation, or infection (see Chapter 49, Arterial Catheterization). Despite these risks, direct blood pressure measurement is often indicated in unstable critically ill patients.[2,8]

6.4.3 Indirect Measurement

Indirect blood pressure measurement techniques are generally less expensive, less time consuming, and less technically demanding. However, they are usually less accurate in very small animals or those suffering from hypotension, peripheral edema, vasoconstriction, and arrhythmias. Although there are multiple methods for measuring blood pressure indirectly, all involve placing a pressure cuff device over the artery. To maximize accuracy, the appropriate-sized cuff must be used (width should be 40% of the circumference of the leg). The different techniques have various benefits and disadvantages that will be discussed with a description of each.

6.4.3.1 Doppler Ultrasonography

Doppler ultrasonography involves using a piezoelectric crystal placed on a peripheral artery to determine flow throughout that artery. Shaving the area and using ultrasonography gel on the probe ensure adequate contact over the artery. The crystal probe is connected to an amplifier that converts the ultrasonic waves to sound waves. A blood pressure cuff connected to a sphygmomanometer is then placed proximal to the probe, and the cuff is inflated until the artery is fully occluded, causing a loss of sound. The pressure of the cuff is reduced slowly and when the sound returns, the pressure of the cuff correlates to the SAP. The pressure at which the sound does not change is theoretically equal to DAP. However, this is a very subjective method for determining diastolic pressure.[2,8]

The Doppler method is the most accurate of the indirect methods for patients that are hypotensive or weigh less than 10 kg. Other advantages include lower cost and portability. Disadvantages include the inability to determine DAP, and thus MAP, and inaccurate readings in smaller animals compared with direct measurement. Values obtained with this method in cats may be lower by 10 to 15 mm Hg than SAP obtained from direct methods, and may therefore more closely approximate MAP.[2,8,9]

6.4.3.2 Oscillometric Sphygmomanometry

Oscillometric sphygmomanometry involves the connection of a cuff to a device that detects oscillations produced by changes in artery wall diameter during blood flow. Inflating the cuff collapses the artery. As the cuff is deflated, the amplitude of the oscillations increases at systolic pressure, reaches a maximum at MAP, and decreases at the diastolic pressure. The MAP is typically measured, but the systolic and diastolic pressures are calculated. Most machines have an automatic timer for performing repeated measurements and an alarm for dangerously low or high readings. Other advantages include ease of use and a measured MAP. Disadvantages are the cost of the machine and decreased accuracy compared with direct measurements. Accuracy is most affected when variation in blood pressure occurs from beat to beat, as seen with stress or with movement. Other causes of inaccuracy include small patient size, vasoconstriction, and arrhythmias.[2,8]

6.4.3.3 Photoplethysmography

Photoplethysmography uses infrared radiation to measure blood volume. This blood volume is held constant by the machine and thus cuff pressure equals intraarterial pressure, with a displayed waveform that is proportional to the strength of the signal. The sensor is designed for human fingertips and therefore may be useful only in small dogs and cats. Also, pigmentation may affect the sensor's ability to acquire an accurate measurement. Advantages include its ability to measure beat-to-beat variation in blood pressure, and disadvantages include its limited usefulness in awake and larger animals.[2,8]

6.5 CLINICAL SIGNIFICANCE OF HYPOTENSION

The clinical signs and significance of hypotension depend on the underlying cause, severity, and duration. In general, decreased blood pressure reduces organ perfusion pressure, although there is not a linear correlation of blood pressure to organ blood flow.[1] The most severe clinical signs are associated with organ failure caused by the decrease in oxygen delivery. Manifestations may include, but are not limited to, acute renal failure, melena, vomiting, arrhythmias, mentation changes, tachypnea, and coagulopathies.

Clinical signs that are seen commonly in hypotensive animals include tachycardia, abnormal pulse quality (weak or bounding), pale mucous membranes, slow capillary refill time, mental dullness, hypothermia, cold extremities, decreased urine output, and weakness.[2] Mucous membranes in dogs with sepsis or systemic inflammatory response syndrome (SIRS) are often injected rather than pale. Cats with hypotension due to sepsis or SIRS often have bradycardia and rarely have injected mucous membranes.[2]

6.6 BASICS OF THERAPY

The most important aspect of treating a hypotensive patient is to address the underlying cause if possible. It is of utmost importance to differentiate between primary cardiogenic causes and other causes of hypotension (Table 6-2). Primary cardiogenic causes such as severe arrhythmias and dilated cardiomyopathy do not respond to fluid therapy, often worsen following fluid administration, and may result in severe pulmonary edema. Cardiogenic causes are often differentiated based on physical examination, thoracic radiography, electrocardiography, and echocardiography. If cardiogenic causes are suspected, specific therapy may include positive inotropic medications, diuretics, and even vasodilatory agents (see Chapter 35, Cardiogenic Shock).

Once primary cardiogenic disease is excluded, the general therapy for hypotension, beyond treating the specific
disease, usually begins with aggressive intravenous fluid therapy. The goal of fluid therapy is to increase preload, 29
stroke volume, and cardiac output and to correct specific deficits (such as anemia), if present (see Chapter 65, Shock 30
Fluids and Fluid Challenge).

Table 6-2 Causes of Hypotension and Recommended Diagnostic Modalities

Cause of Hypotension	Sample Diseases	Diagnostic Modalities
Cardiogenic		
Primary	Cardiomyopathy Valvular disease Arrhythmias SIRS-sepsis Electrolyte abnormalities Severe hypoxia Severe acidosis or alkalosis	*General:* Radiographs, ECG, CBC, serum chemistry analysis *Special:* Echocardiogram, arterial blood gas analysis, pulmonary capillary wedge pressure, CVP
Secondary		
Decreased Preload		
Hypovolemia	Severe dehydration Addisonian crisis Hemorrhage Burns Effusions Pericardial disease Severe pleural disease GDV Caval syndrome	*General:* CBC, serum chemistry analysis, urinalysis, radiographs *Special:* Pericardiocentesis or thoracocentesis, echocardiogram
Decreased venous return		
Decreased Vascular Tone		
—	SIRS—sepsis Electrolyte abnormalities Severe hypoxia Severe acidosis or alkalosis Anaphylaxis Drug or toxins	*General:* CBC, serum chemistry analysis, arterial blood gas analysis *Special:* Systemic vascular resistance index (pulmonary artery catheter and arterial catheter required)

CBC, Complete blood count; *CVP,* central venous pressure; *ECG,* electrocardiogram; *GDV,* gastric dilatation-volvulus; *SIRS,* systemic inflammatory response syndrome.

If the goals of fluid therapy are met and hypotension persists, the cause of hypotension is either secondary cardiogenic or vasodilatory (see Table 6-2). Treatment of secondary cardiogenic hypotension generally requires inotropic support with β-adrenergic agonists (see Chapters 35 and 176, Cardiogenic Shock and Vasoactive Catecholamines, respectively). Conversely, α-agonists or vasopressin are used to manage vasodilatory hypotension (see Chapters 176 and 177, Vasoactive Catecholamines and Vasopressin, respectively). The choice to use either therapeutic strategy is a clinical decision based on whether poor cardiac output or low systemic vascular resistance is predominantly responsible for the hypotension.

Differentiating between vasodilation and decreased contractility is very difficult without a pulmonary artery catheter and or arterial catheter (see Chapter 203, Hemodynamic Monitoring). Some basic tenets that can be suggested are that low vascular resistance often is accompanied by hyperemic mucous membranes and warm extremities. Secondary cardiogenic causes tend to cause pale mucous membranes and prolonged capillary refill times, but caution must be exercised because compensatory noncardiogenic shock states often appear similar.

Many diseases that cause vasodilation can cause decreased cardiac contractility or vice versa. With that in mind, the decision to manage with an inotrope or vasopressor is often empiric. The decision can be made easier by considering the possible benefits and consequences. If a positive inotrope is given to an animal with vasodilatory shock, potential consequences include arrhythmias and/or vasodilatation. Alternatively, using a vasopressor when decreased cardiac contractility is present will worsen cardiac output by increasing afterload. Clinical judgment and response to empiric therapy are often used to guide vasopressor therapy. Mixed α-agonist and β-agonist therapy may be necessary in animals with hypotension from both cardiogenic and vasodilatory causes.

6.7 CONCLUSION

Understanding hypotension requires knowledge of physiologic regulatory mechanisms and determinants of blood pressure. These control mechanisms reveal how the body responds to diseases that can cause hypotension and how the veterinarian can best treat these patients. Ultimately the treatment for hypotension is to treat the underlying disease. However, the initial treatment for hypotension is often supportive. The appropriate supportive therapy will focus on increasing cardiac output, systemic vascular resistance, or both.

6.8 SUGGESTED FURTHER READING*

MF Costello, CM Otto, LJ Rubin: The role of tumor necrosis factor-α (TNF-α) and the sphingosine pathway in sepsis-induced myocardial dysfunction. *J Vet Emerg Crit Care*. **13**, 2003, 25, *An overview of sepsis-induced myocardial dysfunction as a cause of decreased perfusion and hypotension with a focus on one pathway for this phenomenon, although all pathways may have similar results.*

AC Guyton, JE, Hall (Eds.): *The textbook of medical physiology*. ed 10, 2000, Saunders, Philadelphia, *The "bible" of medical physiology textbooks with multiple chapters on blood pressure physiology and controls in Unit IV, The Circulation.*

DW Landry, JA Oliver: The pathogenesis of vasodilatory shock. *N Engl J Med*. **345**, 2001, 588, *A good review of the mechanisms and potential treatment of vasodilatory shock as seen in sepsis and other diseases.*

J Prittie: Optimal endpoints of resuscitation and early goal-directed therapy. *J Vet Emerg Crit Care*. **16**, 2006, 329–339, *Article that discusses the use of end points for resuscitation, with a portion discussing the utility of blood pressure monitoring.*

JS Wohl, TP Clark: Pressor therapy in the critically ill patient. *J Vet Emerg Crit Care*. **10**, 2000, 21, *Good review of vasopressors for veterinary patients.*

* See the CD-ROM for a complete list of references

7 Chapter 7 Oliguria

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7.1 KEY POINTS

- Oliguria is defined as a decrease in urine production below the minimal acceptable rate of 1 to 2 ml/kg/hr.
- Oliguria can occur as a normal physiologic response or as a manifestation of pathology within the renal system.
- Differentiating between physiologic and pathologic oliguria is essential to making appropriate clinical decisions and assessing the severity of disease.
- Physiologic oliguria is usually characterized by a high urine specific gravity and maximal reabsorption of urine sodium.
- Pathologic oliguria resulting from renal failure is characterized by an inappropriately isosthenuric urine and an increase in fractional excretion of sodium.
- Pathologic oliguria usually is seen with severe renal impairment but also can be seen when urine cannot be eliminated from the body.

7.2 INTRODUCTION

Oliguria is defined as abnormally small production of urine. Normal urine output for the dog and the cat is 1 to 2 ml/kg/hr.[1] Oliguria has been defined as urine output ranging from less than 0.27 ml/kg/hr to less than 1 to 2 ml/kg/hr.[1] Oliguria can be classified as prerenal, renal, or postrenal and may represent either an appropriate physiologic response or a pathophysiologic process. It is essential to differentiate physiologic from pathologic oliguria when making clinical decisions and assessing the severity of disease in a critically ill patient.

7.3 PHYSIOLOGIC OLIGURIA

Physiologic oliguria is an appropriate decrease in urine production in response to physiologic stimuli (Box 7-1). When considering the causes of physiologic oliguria, the concept of effective circulating volume (ECV) is paramount. The ECV refers to the portion of extracellular fluid that is in the arterial circulation and is effectively perfusing tissues. A useful physiologic reflection of ECV is the pressure perfusing the arterial baroreceptors, because changes in pressure (or stretch), rather than volume or flow, is generally perceived at these sites.[2] Reductions in ECV, due to either true loss of volume (i.e., hypovolemia) or perceived low volume (i.e., decreased cardiac output), result in the same physiologic responses.[3]

The ECV is sensed in a variety of locations in the body, including baroreceptors in the aortic and carotid bodies, as well as the afferent arterioles of the kidney.[2] For example, when the ECV is decreased in a hypovolemic animal, the subsequent decrease in baroreceptor stimulation results in a number of physiologic responses. The first and most rapid response is mediated by the sympathetic nervous system and is manifested by an increase in heart rate, contractility, and systemic vascular resistance. In addition to these immediate changes, there is also an increase in the secretion of renin, angiotensin II, arginine vasopressin, and aldosterone. Increased reabsorption of sodium and water, as well as additional vasoconstriction, results. There is also an increase in thirst, which serves to further augment ECV if the patient drinks water.

7.3.1 Box 7-1 Causes of Oliguria

7.3.1.1 Prerenal Oliguria

- Hypovolemia
- Dehydration
- Blood loss
- Third space losses
- Decreased cardiac output
- Congestive heart failure
- Cardiac tamponade
- Sepsis
- Vasodilation
- Sepsis
- Cirrhosis
- Nephrotic syndrome
- Vasodilatory drugs

7.3.1.2 Renal Oliguria

- Acute tubular necrosis
- Ischemia

Nephrotoxicity

Chronic renal failure (end stage)

7.3.1.3 Postrenal Oliguria

Ureteral obstruction

Urethral obstruction

Urinary tract rupture

Oliguria that occurs in response to a decrease in ECV is an appropriate physiologic response and is not a result of acute renal failure. It is important to remember that although this response to a decrease in ECV is appropriate, it may prove maladaptive in certain clinical situations, such as congestive heart failure. In most instances of physiologic oliguria, a urinalysis will reveal a maximally concentrated urine (specific gravity >1.040) and a fractional excretion of sodium of less than 1%.[2,4-6] However, these changes may not be present if the animal has been receiving diuretics (e.g., furosemide or mannitol), has inappropriate neurohormonal abilities (e.g., hypoadrenocorticism), or suffers from a disease causing hyperosmolality (e.g., diabetes mellitus). 31

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7.4 PATHOLOGIC OLIGURIA

Pathologic oliguria typically is seen with severe renal injury. The decrease in urine output in this instance is a reflection of the decrease in glomerular filtration rate (GFR) in the profoundly diseased kidney. Postrenal diseases such as urethral obstruction can also result in oliguria.[1,4] In addition to the common causes for postrenal obstruction, such as stones or mucous plugs, less common causes including neoplasia, strictures, and urinary bladder herniation should be considered.[6]

The first task for the clinician is to determine whether oliguria is pathologic or nonpathologic. As discussed earlier, patients with physiologic oliguria have decreased urine output as a result of maximal water and sodium reabsorption by the kidney. With renal failure–induced oliguria, there is a decrease in GFR and often a defect in sodium reabsorption. In animals with acute tubular necrosis, a number of pathologic processes contribute to the impairment of renal function and the ultimate decrease in GFR and urine output. These include increases in tubular cell apoptosis, sloughing of tubular cells into the tubular lumen, alterations in tubular cell membrane polarity, loss of the integrity of tight junctions between renal tubular cells, increased intracellular calcium concentration, obstruction of tubular lumens with cellular debris and sloughing tubular cells (these form the coarse granular casts that are a hallmark of acute tubular necrosis), an increased number of inflammatory mediators, and alterations of renal vascular tone[7] (see Chapter 135, Acute Renal Failure).

7.5 APPROACH TO THE OLIGURIC PATIENT

When evaluating a patient with suspected oliguria, the volume of urine output must first be determined. This is best accomplished by performing a quantitative measurement of urine output using a closed urine collection system. If this is not possible, useful information can be gleaned using frequent evaluations of the patient's weight and measurements of urine voided onto diapers (by weight). If urine output is found to be less than 1 to 2 ml/kg/hr, the clinician must determine if the observed oliguria is physiologic or pathologic. An assessment of the physical parameters of volume status such as skin turgor and mucous membrane moisture may be helpful, but it is important to remember their limitations.[8] If a closed urinary collection system is in place, it should be assessed to confirm that it is patent and positioned properly. Mean arterial blood pressure should be measured; a decrease in the mean arterial blood pressure below 70mm Hg will result in a decrease in both renal blood flow and GFR.[2] This prerenal decrease in renal perfusion will result in a decrease in urine output, but it does not equate to acute renal failure. Measurements of lactate levels, capillary refill time, and core-toe web temperature will provide information about perfusion that can be helpful in determining the difference between prerenal and renal oliguria. In animals with questionable volume status, central venous pressure monitoring may also be used to guide fluid therapy. (See Chapter 203, Hemodynamic Monitoring.)

One of the most useful laboratory tests in the evaluation of an oliguric patient is the urinalysis. A full urinalysis, including both urine dipstick testing and sediment evaluation, should be performed. In addition, the calculation of fractional excretion of sodium may be of great value (Box 7-2). In any critically ill patient, it is prudent to submit a urine culture in addition to the urinalysis because pyelonephritis can lead to acute renal failure. Animals with a decreased ECV will frequently have a high urine specific gravity (>1.035). In addition, the fractional excretion of sodium is usually <1.0%; this reflects the drive to maximally reabsorb sodium, and thus water, to augment the ECV. By contrast, the patient with renal oliguria will have an isosthenuric urine and an increase in fractional excretion of sodium.[4-7] This reflects a tubular insult or neurohormonal dysfunction that has caused impaired water and sodium reabsorption. The urine fractional excretion of sodium is a useful test, but there can be overlap in patients that have received diuretics, suffer from a hyperosmolal disease state (e.g., diabetes mellitus), or have acute tubular necrosis in addition to a chronic disease that promotes sodium reabsorption.[4,5,7] Other indicators of acute tubular necrosis include glucosuria despite a normal blood glucose concentration and the presence of coarse granular casts within the urine sediment. Proteinuria and hematuria may also be present.[6,7]

7.6 INTERVENTIONS FOR THE OLIGURIC PATIENT

When caring for a patient with physiologic oliguria, treatment should be tailored to the underlying problem (see Chapters 135 and 180, Acute Renal Failure and Diuretics, respectively). For example, if the animal is dehydrated secondary to severe vomiting and diarrhea, therapy should be directed at replacing the volume deficits and correcting the cause of the vomiting and diarrhea. If a decrease in cardiac output is suspected, therapy should be directed toward that process.

A variety of management strategies have been recommended for renal oliguria. A great deal of effort has been focused on interventions that convert oliguria to nonoliguria, because oliguria is a negative prognostic indicator and is difficult to manage medically.[9] One of the mainstays of therapy in the oliguric patient has been loop diuretics such as furosemide. The logic behind this therapy is that increasing the volume of ultrafiltrate in the tubular lumen will help to flush out tubular debris that otherwise may obstruct the lumen and contribute to further damage. In addition, because furosemide inhibits the Na^+-K^+-$2Cl^-$ pump of the ascending limb of the loop of Henle, it was thought that the subsequent decrease in renal tubular energy requirements would also be of benefit. Many studies have been done to investigate the usefulness of furosemide, but none of them has shown a clear therapeutic benefit.[9]

A second commonly used therapy for the oliguric patient is the osmotic diuretic mannitol. Like furosemide, mannitol increases the volume of ultrafiltrate and thus may be of benefit in flushing debris from the tubular lumen. 32 33

In addition, mannitol has free-radical scavenging capabilities. The production of oxygen free-radical species has been implicated in the progression of acute tubular necrosis, so scavenging of these agents would theoretically be of benefit.[1,7] No human or veterinary clinical trials have shown this to be the case.[1] Mannitol should be used with caution because it can result in aggressive expansion of the vascular volume and volume overload if it is not excreted.

7.6.1 Box 7-2 Calculation of the Fractional Excretion of Sodium

$$FE_{Na} = \frac{U_{Na} \times P_{Cr}}{P_{Na} \times U_{Cr}} \times 100$$

FE_{Na} = fractional excretion of sodium

U_{Na} = urine sodium concentration

P_{Cr}= plasma creatinine concentration

P_{Na}= plasma sodium concentration

U_{Cr}= urine creatinine concentration

A final treatment of the oliguric patient has traditionally been dopamine. Dopamine is a catecholamine that exerts dopaminergic as well as α-adrenergic and β-adrenergic effects. In both human and veterinary medicine, low dosage (<5 μg/kg/min) administration has been advocated to increase renal blood flow and urine output, with the goal of either preventing or reversing oliguria.[1] Unfortunately, the theoretical benefits of dopamine have not been realized clinically and the recommendation in the human literature is against the use of dopamine at a “renal dosage.”[5,7] There are no clinical trials investigating the efficacy of dopamine in veterinary patients with renal failure.

Additional therapies under investigation for the treatment of acute renal failure include fenoldopam (a selective DA-1 receptor agonist),[10] calcium channel blockers (diltiazem), and atrial natriuretic peptide.[1,5] At this time, there is insufficient evidence to recommend their use in veterinary medicine.

Animals that are oliguric despite medical therapy may require dialysis as a lifesaving measure (see Chapter 137, Hemodialysis and Peritoneal Dialysis).

7.7 SUGGESTED FURTHER READING*

DJ Chew, JA Gieg: Fluid therapy during intrinsic renal failure. In SP DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 3, 2006, Elsevier, St Louis, *Gives useful information on what constitutes oliguria and the treatment strategies for reversing it.*

CA Osborne, JB Stevens, JP Lulich, et al.: A clinician's analysis of urinalysis. In CA Osborne, DR Finco (Eds.): *Canine and feline nephrology and urology*. 1995, Williams & Wilkins, Baltimore, *A great reference for small animal nephrology; easy to read and clinically relevant.*

BD Rose, TW Post: In *Clinical physiology of acid-base and electrolyte disorders*. ed 5, 2001, McGraw-Hill, New York, *An excellent discussion of the physiologic mechanisms that control effective circulating volume.*

RW Schrier, W Wang, B Poole, et al.: Acute renal failure: Definitions, diagnosis, pathogenesis and therapy. *J Clin Invest*. **114**, 2004, 5, *An excellent review of acute renal failure with an in-depth discussion of the underlying pathophysiology*.

* See the CD-ROM for a complete list of references

8 Chapter 8 Deteriorating Mental Status

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8.1 Key Points

- Consciousness is maintained by the cerebral cortex and the brainstem's reticular activating system.
- Abnormalities in mentation may be seen with metabolic disease, drug administration or toxicity, and structural brain disease.
- Metabolic disease, drugs, or toxins usually cause signs of diffuse cerebral dysfunction.
- Structural disease or injuries typically affect the brainstem or unilateral cerebrum or thalamus.
- Five patient evaluation parameters that will aid in lesion localization and prognosis for recovery include: (1) level of consciousness, (2) motor activity, (3) respiratory patterns, (4) pupil size and reactivity, and (5) oculocephalic reflex.
- Frequent reassessment of the patient with deteriorating mental status permits detection of changes that may require intervention.

8.2 INTRODUCTION

Altered mentation in patients, whether rapidly or slowly progressive, is of particular concern to the clinician in the intensive care unit. It is seen with primary neurologic disease, neurologic complications of other diseases, many systemic diseases, and with some drugs.[1] A decline in mental status is characterized by decreasing responsiveness and interaction with the environment, although agitation and hyperreactivity can also indicate neurologic dysfunction. Rapid neurologic assessment of the declining patient, coupled with knowledge of underlying disease and medication, will permit the formulation of a list of possible causes, diagnostic and therapeutic plans, as well as an estimation of prognosis.

8.3 STATES OF CONSCIOUSNESS

8.3.1 Normal

The animal has a normal demeanor and interaction with its environment. “Normal” varies among animals, and the clinician relies on the client's knowledge of the pet's behavior, as well as the initial neurologic evaluation. For example, docile behavior in a cat, which most clinicians would consider desirable, may be very abnormal if the owner reports the cat is typically fearful and aggressive.

8.3.2 Obtunded

Obtundation is a state of decreased responsiveness or alertness and is graded as mild, moderate, or severe. Lethargy is similar, reflecting decreased level of consciousness with listlessness and drowsiness. Other terms commonly used to describe altered mentation in humans, such as confusion, delirium, and dementia, are difficult to extrapolate to veterinary medicine because these states are characterized by disorientation to time and place, loss of memory, and disorganized speech, which are difficult to impossible to evaluate in the veterinary patient.[2,3]

8.3.3 Stupor or Semicoma

The patient responds only to vigorous or painful stimuli.

8.3.4 Coma

The patient does not respond consciously to any stimuli. Segmental spinal reflexes will be present (in the absence of additional lesions) and possibly exaggerated, and cranial nerve reflexes may be present, depending on the location of the lesion causing the coma.[3,4]

8.4 NEUROANATOMY

Abnormalities in mentation indicate either dysfunction of the reticular activating system in the brain stem or dysfunction of the cerebrum.

8.4.1 Cerebrum

The cerebrum is the region of the brain responsible for the integration of sensory information from the entire body, planning of motor activity, and appropriate responses to this information, emotion, and memory. Functionally distinct regions are present in the cerebral cortex (e.g., occipital lobe associated with vision; temporal lobe associated with auditory function).[5]

8.4.2 Reticular Activating System

The ascending reticular activating system (RAS), or reticular formation, is a network of anatomically and physiologically distinct nuclei in the brain stem that function to “activate” the cerebral cortex and maintain consciousness.[6] Experimentally, stimulation of the RAS in anesthetized cats produced electroencephalogram patterns consistent with the conscious state.[7]

Numerous nuclei in the reticular activating system have projections to the cerebrum, but those in the midbrain, rostral pons, and thalamus are the most important for maintaining consciousness.[2,8] In anesthetized cats, transection of the brain stem at the level of the pons and midbrain produced coma, but transection at the junction of the medulla and cervical spinal cord did not.[9]

8.5 ETIOLOGY OF LESIONS

Lesions causing changes in mentation will be structural, metabolic, or toxic in origin. Clinical signs of diffuse cerebral disease with normal brain stem function are most common with metabolic disease, toxins, or drugs affecting the cerebrum globally (Boxes 8-1 and 8-2). Seizures indicate cerebral cortical dysfunction caused by either 34 extracranial or intracranial disease (see Chapter 98, Seizures and Status Epilepticus). 35 Impairment of the brain stem or thalamus, as well as lateralized cerebral dysfunction (e.g., compulsive circling in one direction, unilateral cortical blindness), is more likely the result of structural disease or injury (Box 8-3).

8.5.1

Box 8-1 Common Metabolic Diseases That May Cause Altered Mentation[2,6]

- Hypoxia (anemia, pulmonary disease, methemoglobinemia)
- Ischemia (cardiac disease, postarrest, hyperviscosity, systemic embolic disease)
- Hypoglycemia
- Hepatic disease (hepatic encephalopathy)
- Renal failure (uremic encephalopathy)
- Endocrine dysfunction (hyperfunction or hypofunction)
  - Pituitary (apoplexy)
  - Thyroid
  - Adrenal (hypoadrenocorticism, pheochromocytoma)
  - Pancreas (diabetes mellitus, especially hyperosmolar)
- Sepsis
- Hyperbilirubinemia (kernicterus)
- Hyperthermia or hypothermia
- Pain
- Central nervous system diseases
  - Continuous seizure activity
  - Postictal state
  - Diffuse meningitis or encephalitis
- Electrolyte or acid-base abnormalities
  - Sodium or water
  - Magnesium
  - Calcium
  - Acidosis (metabolic or respiratory)
  - Alkalosis (metabolic or respiratory)

8.5.2

Box 8-2 Common Drugs That May Cause Altered Mentation[1,2,10]

- Anticonvulsants (barbiturates, bromides)
- Benzodiazepines
- Opiates
- Anesthetic drugs
- Atropine
- Antibiotics (penicillin, cephalosporins, quinolones, aminoglycosides, metronidazole)
- Steroids
- Histamine-2 receptor blockers
- Cardiac glycosides (digitalis)
- Antihypertensives (hydralazine, ACE inhibitors)
- Illicit substances (cannabis, cocaine, amphetamines)

ACE, Angiotensin-converting enzyme.

8.6

EVALUATION

Basic neurologic evaluation of the patient with altered mentation includes assessment of five physiologic variables: (1) level of consciousness or mentation, (2) motor activity, (3) respiratory patterns, (4) pupil size and reactivity, and (5) oculocephalic movements.[2] Coma scales are based on information obtained from these assessments (see Chapter 97, Coma Scales), and knowledge of the pathophysiology affecting these variables will aid in lesion localization and determining progression of disease.

8.6.1

Level of Consciousness

As discussed previously, mentation abnormalities result from structural or metabolic disease affecting the cerebrum or reticular activating system or both. Grading of mentation from normal to comatose and any details specific to the individual patient should be described (e.g., readily opens eyes when name is called).

8.6.2

Motor Activity

The patient may be ambulatory or nonambulatory and may have generalized ataxia, hemiparesis, tetraparesis, or hemiplegia. Obvious gait abnormalities with paresis or paralysis are more indicative of a lesion at, or caudal to, the midbrain, and deficits are ipsilateral to the lesion. Patients with mild or moderate lesions rostral to the midbrain often have minimal gait abnormalities or paresis, although contralateral proprioceptive reactions are absent.[4]

Decerebrate and decerebellate postures are associated with lesions in specific brain regions. Decerebrate rigidity is seen with lesions of the rostral pons and midbrain. Opisthotonus with extensor rigidity of all four limbs is present, and mentation is stuporous to comatose. Decerebellate rigidity may occur with acute cerebellar lesions. Opisthotonus with extensor rigidity of the thoracic limbs and either extension or flexion of the pelvic limbs is present, depending on the location of the cerebellar lesion; the patient should be responsive and have voluntary movement.[3,4]

8.6.2.1 Box 8-3 Structural Lesions That May Alter Mentation

- Neoplasia (primary, secondary)
- Infection (bacterial, fungal, protozoal, viral)
- Inflammation, noninfectious
  - Granulomatous meningoencephalomyelitis
  - Necrotizing encephalitis
- Trauma (hemorrhage, edema, diffuse axonal injury)
- Vascular lesions (infarction, hemorrhage)
- Hydrocephalus, especially if resulting from acute obstruction of cerebrospinal fluid
- Shifts of intracranial structures (herniation), secondary to any of the above

8.6.3 Respiratory Patterns

Some respiratory patterns are associated with lesions in certain areas of the brain (Box 8-4). Animals with brain stem lesions causing respiratory changes have a guarded to poor prognosis.[4] Other diseases must be considered in patients with abnormal ventilation. Hyperventilation can be seen with diabetic ketoacidosis, uremia, hepatic failure, sepsis, and pneumonia. Hypoventilation may result from administration of sedative drugs (especially opiates), generalized neuromuscular disease, and pulmonary disease.[2]

8.6.4 Pupil Size and Reactivity

Pupil size is the result of balance between sympathetic and parasympathetic innervation to the eye. Parasympathetic innervation is particularly important when evaluating for neurologic deterioration because it is mediated through the midbrain and cranial nerve III (loss of parasympathetic innervation results in mydriasis).[4] Most abnormalities of pupil size and pupillary light reflexes are the result of structural lesions of the brain,[6] but metabolic encephalopathies and some drugs (benzodiazepines, opiates) can cause bilateral miosis, whereas parasympatholytic agents (atropine) may cause mydriasis[1,4] (Box 8-5).

8.6.5 Oculocephalic Reflex

Physiologic nystagmus, or “doll's eye” reflex, consists of conjugate eye movements in response to vestibular input 35
(turning the head from side to side). Loss of the oculocephalic reflex occurs with lesions of the medial 36
longitudinal fasciculus in the pons and midbrain, which coordinates functions of cranial nerves III, IV, and VI, which innervate the extraocular eye muscles, and usually indicates a poor prognosis.[4] Lesions of the individual nuclei or cranial nerves III, IV, or VI will also result in an abnormal oculocephalic reflex, but a persistent, nonpositional strabismus will be present in the affected eye.[3] Extreme caution should be taken when manipulating the heads of patients with a history of trauma, until cervical fractures or luxations have been ruled out.

8.6.5.1 Box 8-4 Respiratory Patterns Associated With Intracranial Lesions[1,2,6]

Cheyne-Stokes breathing: Periods of hyperpnea alternating with periods of apnea. Can be seen with diffuse cerebral or thalamic disease and metabolic encephalopathies.

Central neurogenic hyperventilation: Persistent hyperventilation that may result in respiratory alkalosis. Associated with midbrain lesions.

Apneusis: Breathing pauses for a period at full inspiration. Associated with pontine lesions.

Irregular or “ataxic” breathing: Irregular frequency and depth of respiration that typically precedes complete apnea. Associated with lesions of lower pons and medulla.

8.6.5.2 Box 8-5 Pupillary Abnormalities and Lesion Localization[1,4]

Unilateral mydriatic, unresponsive pupil: Loss of parasympathetic innervation to the eye. Indicates destruction or compression of the ipsilateral midbrain or cranial nerve III, often associated with increased intracranial pressure and unilateral cerebral herniation. Rule out unilateral topical ophthalmic atropine or tropicamide.

Bilateral miosis: Can be seen with metabolic encephalopathies or diffuse midbrain compression with increased intracranial pressure, and may precede mydriatic, unresponsive pupils.

Bilateral, mydriatic, unresponsive pupils: Fixed and dilated pupils. Severe, bilateral compression or destruction of the midbrain or cranial nerve III, typically from bilateral cerebral herniation. Grave prognosis.

8.7 DIAGNOSTIC APPROACH

In all patients with abnormal mentation, the clinician should initially assess systemic and metabolic stability. When patients arrive in the ICU acutely ill, physical examination and historical information such as drug exposure, previous or ongoing illness, and possible trauma are invaluable to determining the cause of mentation abnormalities. Routine blood work will evaluate acid-base status, electrolyte values, hematocrit, and liver and kidney function. Additional tests or blood work should be done based on suspicion of underlying disease. Once systemic disease is ruled out and a lesion is localized to the brain, specific neurodiagnostic tests, particularly intracranial imaging with magnetic resonance imaging or computed tomography, and cerebrospinal fluid analysis should be pursued as indicated.

For patients in the ICU with nonneurologic disease that experience a deterioration in mentation, the status of their underlying disease and metabolic state must be reassessed for any recent changes. If no changes have occurred, then neurologic complications of the primary disease should be considered (e.g., vascular event).

For patients in the ICU with known structural brain disease, the most life-threatening cause for a decline in mentation is increased intracranial pressure and herniation of brain structures. Infarction or hemorrhage secondary to the underlying brain lesion is also possible.

8.8 TREATMENT

Because so many systemic and neurologic diseases can cause abnormal mentation, treatment will be based on the underlying cause. If toxin exposure or drug reaction is suspected, supportive care and withdrawal of medication is indicated. The patient's metabolic parameters should be maintained within normal ranges, and in patients with brain disease and suspected increased intracranial pressure, aggressive medical therapy should be instituted (see Chapter 100, Intracranial Hypertension). Most importantly, vigilant and repeated assessment of the patient with altered mental status by the ICU clinicians and staff will permit early detection of changes so that appropriate diagnostic and therapeutic intervention can be implemented.

8.9 SUGGESTED FURTHER READING*

A DeLahunta: In *Veterinary neuroanatomy and clinical neurology*. ed 2, 1983, Saunders, Philadelphia, Classic veterinary neuroanatomy text with excellent basic science detail, as well as practical applications for patients.

MD Lorenz, JN Kornegay: In *Handbook of veterinary neurology*. ed 4, 2004, Saunders, Philadelphia, *Classic, practical veterinary neurology text. Essential for basic neuroanatomy and neurology*.

C Saper: Brain stem modulation of sensation, movement, and consciousness. In E Kandel, JH Schwartz, TM Jessel (Eds.): *Principles of neural science*. ed 4, 2000, McGraw-Hill, New York, *Detailed scientific discussion of brainstem nuclei and practical patient evaluation; excellent reference text.*

C Saper, S Iversen, R Frackowiak: Integration of sensory and motor function: The association areas of the cerebral cortex and the cognitive capabilities of the brain. In E Kandel, JH Schwartz, TM Jessel (Eds.): *Principles of neural science*. ed 4, 2000, McGraw-Hill, New York, *Very detailed basic science chapter on cerebral function and cognition in an excellent reference text on neuroscience.*

* See the CD-ROM for a complete list of references

9 Chapter 9 Tachypnea and Hypoxemia

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9.1 KEY POINTS

- Tachypnea may occur with or without hypoxemia in critically ill animals.
- The diagnostic and therapeutic plan is different for patients with tachypnea and hypoxemia than for those with tachypnea in the absence of hypoxemia.
- Diagnostic tests, and even physical examination, may have to wait until a patient has been sedated and stabilized with supplemental oxygen.
- To develop a rational diagnostic and management plan, clinicians should refine their list of differential diagnoses and localize the problem by thorough history of the current illness, signalment, and observation of the patient's breathing pattern.
- The primary mechanisms of hypoxemia include the following: (1) decreased partial pressure of oxygen in the inspired air, (2) hypoventilation, (3) ventilation-perfusion (V_A/Q) mismatch, (4) shunt, and (5) diffusion impairment.

9.2 INTRODUCTION

An increased respiratory rate or tachypnea is almost always evident in the patient with respiratory distress, but the causes of tachypnea are numerous and it may or may not reflect respiratory tract disease. When developing an appropriate therapeutic and diagnostic plan, it is essential to differentiate between tachypneic patients with and those without concurrent hypoxemia. Hypoxemia can be detected with pulse oximetry or arterial blood gas analysis (see Chapter 208, Blood Gas and Oximetry Monitoring).

9.3 TACHYPNEA WITHOUT HYPOXEMIA

Respiratory rate is controlled by the respiratory center in the brainstem in response to numerous afferent pathways, both central and peripheral in origin. These include the cerebral cortex, central chemoreceptors, peripheral chemoreceptors, stimulation of mechanoreceptors in the airways that sense lung inflation and deflation, stimulation of irritant receptors of the airways and stimulation of C-fibers in the alveoli and pulmonary blood vessels that sense interstitial congestion, and baroreceptors that sense changes in blood pressure.[1] Consequently, numerous disease processes can lead to tachypnea in the absence of hypoxemia. These include hyperthermia, pain and anxiety, brain disease, hypotension, metabolic acidosis, hypercapnia, inhaled irritants, and interstitial lung disease. A thorough history, physical examination, and initial blood test results will allow the clinician to determine which of these disease processes is present in most cases, and therapy should be tailored appropriately.

9.4 TACHYPNEA WITH HYPOXEMIA

When the tachypneic patient is determined to be also hypoxemic, the diagnostic and therapeutic approach will need to be tailored appropriately. Respiratory distress in small animals often presents a therapeutic dilemma. Tachypneic hypoxemic patients can be so compromised that diagnostic tests can stress them to the point of respiratory and cardiac arrest. A diagnosis should not come at the expense of the patient. Restraint for catheterization, radiographs, and physical examination may have to wait until the patient is relaxed and breathing more easily.

When an animal has difficulty oxygenating blood, breathing becomes more labored. Although terms such as *dyspnea* or *anxiety* should be avoided in veterinary medicine (our patients cannot tell us they're having difficulty breathing or fear), we should assume that these patients are experiencing tachypnea and orthopnea associated with hypoxemia. This natural response leads to more complications because the stressed patient needs more oxygen and rapid breathing may not be as efficient as relaxed, normal breathing. For this reason, tranquilizers and sedative drugs may prove very useful in the early treatment of respiratory distress.

Inspired oxygen concentration may be increased using a face mask, nasal cannula, or an induction chamber attached to an anesthesia circuit's oxygen supply. Oxygen cages increase inspired oxygen while allowing the clinician time to observe the patient and localize the problem.

It is important to observe the patient, refine the list of differential diagnoses, and determine the nature of the problem. A rapid, shallow (restrictive) respiratory pattern suggests higher than normal elastic forces within the lung. A deep, noisy (inspiratory) pattern is seen with increased airway resistance from airway obstruction. With a restrictive pattern, auscultation can help differentiate pleural space disease (pneumothorax, hydrothorax) from parenchymal diseases (pneumonia, pulmonary edema). Signalment and history can help determine a cause of airway obstruction (brachycephalic airway disease, history of a cough, playing with small toys).[2-4]

A basic understanding of the work of breathing and mechanisms of impaired gas exchange will help the clinician develop a rational diagnostic and treatment plan.

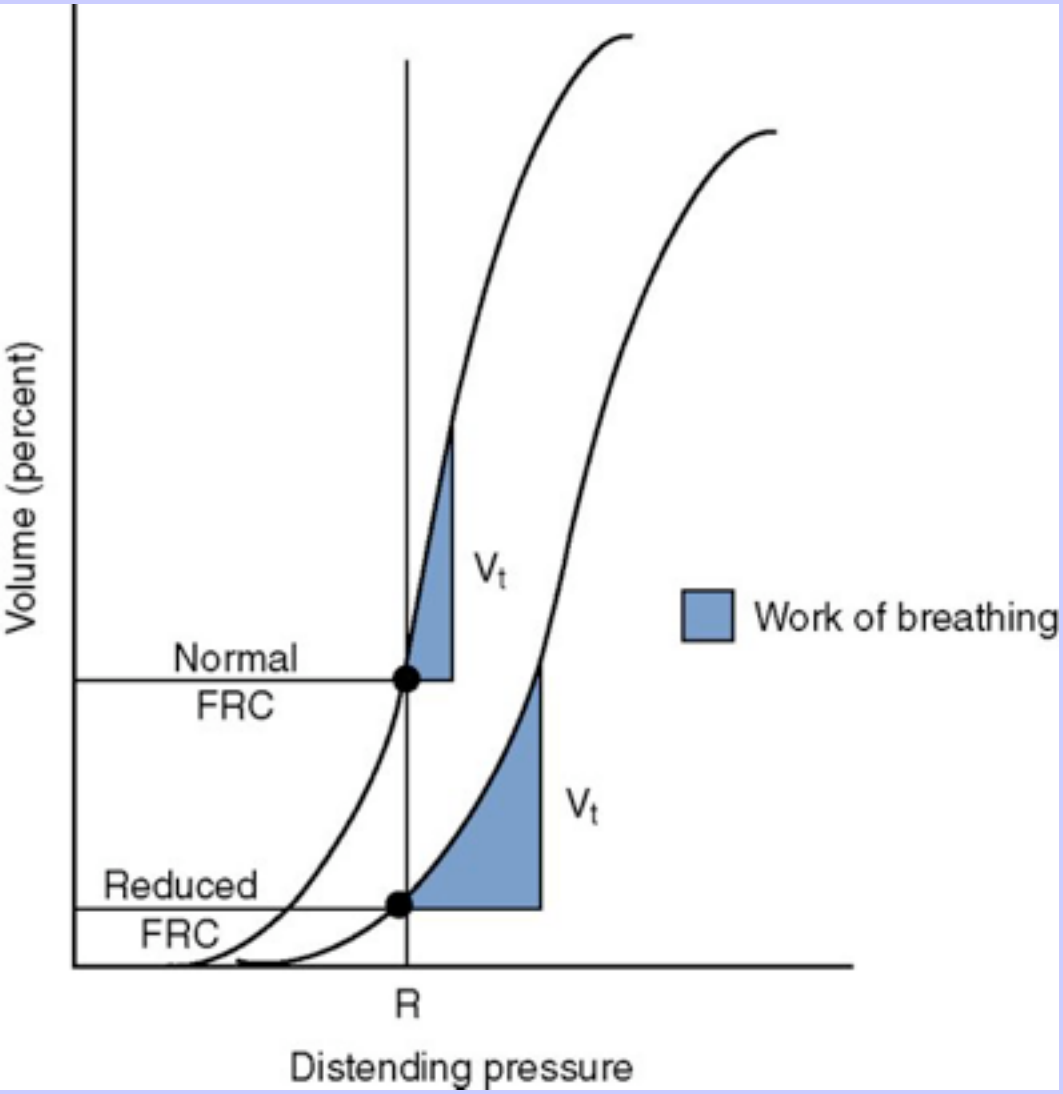
9.5 WORK OF BREATHING

For normal respiration and gas exchange, fresh gas must be brought into the alveoli through the process of alveolar ventilation. The oxygen cost of quiet breathing is extremely small, less than 3% of total resting oxygen consumption. With voluntary hyperventilation (as is seen with respiratory distress), it is possible to increase cost of breathing to 30% of resting oxygen consumption. For animals with obstructive or restrictive lung disease, oxygen cost of breathing can limit their exercise tolerance.[1,5]

Muscles of the respiratory system must overcome two major forces in normal respiration: elastic recoil and airway resistance. The functional residual capacity (FRC) is defined as the volume of air remaining in the lungs after a normal expiration. FRC is the volume of the lungs at rest and is determined by the static properties of the respiratory system.[1,5] Fibrous structures of the lung provide elastic recoil. The fibrous structures of the lung favor pulmonary collapse, while the fibrous structures of the chest wall favor thoracic expansion. The balance between lung elastic recoil and thoracic wall recoil ultimately determines the FRC. The FRC is reduced in patients with reduced lung compliance.[1,5]

To understand how FRC is clinically significant we must understand compliance. Pulmonary compliance is reflected by the slope of the pressure-volume curve (Figure 9-1). The slope of this curve represents the volume change per unit pressure.[1,5] When the slope of this curve is steep, a small change in pressure results in a large change in volume. This makes for efficient ventilation requiring minimal energy to effect gas movement. Diseases affecting pulmonary compliance can increase the work required for normal ventilation. Pulmonary atelectasis, pneumonia, pulmonary edema, fibrosis, and pleural space diseases (causing pulmonary collapse) are examples of conditions resulting in decreased pulmonary compliance.

Figure 9-1 The pressure-volume curve. The steep curve to the left represents a normal lung. At rest *(R)*, the lung volume is a balance between the elastic recoil of the chest wall and the elastic forces of the lung. The lungs are in balance, held open at the steepest portion of the curve. This represents the best pulmonary compliance, where a small change in distending pressure is sufficient to maintain tidal volume (V_t). The curve to the right represents a diseased lung with reduced compliance where the curve and slope of the curve are flatter. This patient needs more distending pressure (work) to effect the same tidal volume. The shaded area represents the work of breathing.



9.6 AIRWAY RESISTANCE

Airway resistance is the pressure difference between the alveoli and the mouth divided by flow rate and is determined by Poiseuille's law: $R = 8\eta l \div \pi r^4$ where R = airway resistance, η = viscosity, l = length, and r = radius. Note the critical importance of tube radius; if the radius is halved, the resistance increases 16-fold. In contrast, doubling the length only doubles resistance. Note also that the viscosity of the gas, but not its density, affects the pressure-flow relationship. The site of most airway resistance is the medium-sized bronchi. The smallest airways contribute very little to resistance, because the combined cross-sectional area of these airways is much larger than that of the intermediate bronchi.[1,5]

Airway resistance is determined by lung volume, bronchial smooth muscle tone, and dynamic airway compression. At lower lung volumes, radial traction supporting the bronchi is lost and airway caliber is reduced. Bronchial muscle contraction narrows airways and increases resistance. Bronchoconstriction is mediated through reflex stimulation of irritant receptors in the upper airways or increased parasympathetic activity. Increased sympathetic tone leads to bronchodilation, as do sympathomimetic drugs such as isoproterenol, epinephrine, and norepinephrine. Dynamic airway collapse is seen with forceful respiration. Sudden changes in intrathoracic pressure can affect the large airways.

9.7 HYPOXEMIA

Hypoxemia occurs when the partial pressure of oxygen in the arterial blood (PaO_2) is less than 80 mm Hg (sea level). There are five primary causes of a reduced PaO_2 in arterial blood:

1. Decreased partial pressure of inspired oxygen (PiO_2)
2. Hypoventilation
3. Ventilation-perfusion (V_A/Q) mismatch
4. Shunt
5. Diffusion impairment

Decreased inspired oxygen, as occurs at high altitudes, causes hypoxemia. In this instance hypoxemia is not due to a pathologic problem. The average barometric pressure (BP) at sea level is 760 mm Hg. PiO_2 is determined by the total BP minus the vapor pressure of water (VP_{H2O}) at body temperature (47 mm Hg at 37° C) times the fraction of inspired oxygen (FiO_2). The FiO_2 of unsupplemented air (room air) is approximately 21%.

$$\begin{aligned}
\mathrm{PiO}_2(\text{sea level}) &= \mathrm{FiO}_2(\mathrm{BP} - \mathrm{VP}_{\mathrm{H_2O}})\\
&= 0.21(760 - 47)\\
&= 150\ \text{mm Hg}\\
\mathrm{PiO}_2(5000\ \text{ft}) &= \mathrm{FiO}_2(\mathrm{BP} - \mathrm{VP}_{\mathrm{H_2O}})\\
&= 0.21(640 - 47)\\
&= 124\ \text{mm Hg}
\end{aligned}$$

Animals living at higher altitudes will compensate by increasing alveolar ventilation. The result is normal oxygenation with a lower partial pressure of carbon dioxide (PCO_2), or mild hyperventilation.[5]

A low PiO_2 can also occur when an animal is connected to a breathing circuit, such as an anesthesia machine, if the 38
oxygen supply to the patient is interrupted. The oxygen source should be the first thing that is evaluated when 39
hypoxemia is identified in the patient on a breathing circuit.

Hypoventilation results in less fresh gas reaching the alveoli (decreasing alveolar ventilation). By bringing less fresh air to the alveoli to dilute waste gases, hypoventilation causes a rise in blood PCO_2; an elevated PCO_2 is by definition hypoventilation. Because the gas exchange surfaces in the lungs are normal, hypoxemia from hypoventilation is corrected by increasing the FiO_2 with supplemental oxygen. There is a linear relationship between PCO_2 and PaO_2. As the PCO_2 rises (hypoventilation), PaO_2 falls. A function of the respiratory exchange ratio, this inverse linear relationship is nearly 1:1. For every torr (mm Hg) the PCO_2 goes up, PaO_2 will go down approximately 1 torr. Arterial PO_2 can fall to extremely low levels only if severe hypoventilation occurs in the patient that is breathing room air.[1,5] Another important metabolic consequence of extreme hypoventilation is respiratory acidosis.

Ventilation-perfusion (V_A/Q) mismatch occurs when ventilation and blood flow are not closely matched in gas exchange units. Normally ventilation and perfusion are closely matched so that blood is directed to well-ventilated alveoli (Figure 9-2). When the V_A/Q is not matched, the result is inefficient gas exchange. Regions of the lung that receive more ventilation than perfusion (high V_A/Q) tend to increase the PaO_2, while areas that receive less ventilation than perfusion (low V_A/Q) will contribute to a lower PaO_2. If regions of the lung are not ventilated at all but are perfused (i.e., the extreme of low V_A/Q), the functional result is a shunt. Pulmonary conditions that cause incomplete alveolar collapse (pneumonia, pulmonary edema, atelectasis) are the most common cause of low V_A/Q.[4,5] Hypoxic pulmonary vasoconstriction describes a reflex vasoconstriction of pulmonary vessels in response to low alveolar oxygen tension. This compensatory reflex serves to reduce perfusion to poorly ventilated alveoli, improving V_A/Q matching and optimizing gas exchange (see Figure 9-2).[4,5]

Figure 9-2 Normal V_A/Q relationship. On the left, normal ventilated alveoli are all perfused equally. On the right, when the second lung unit from the left has reduced ventilation, a corresponding decrease in perfusion (hypoxic pulmonary vasoconstriction) improves the V_A/Q relationship.

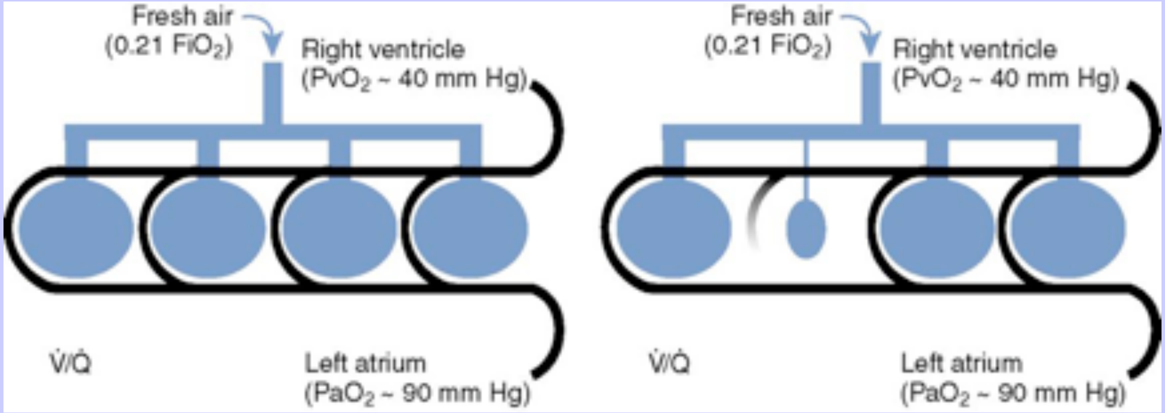
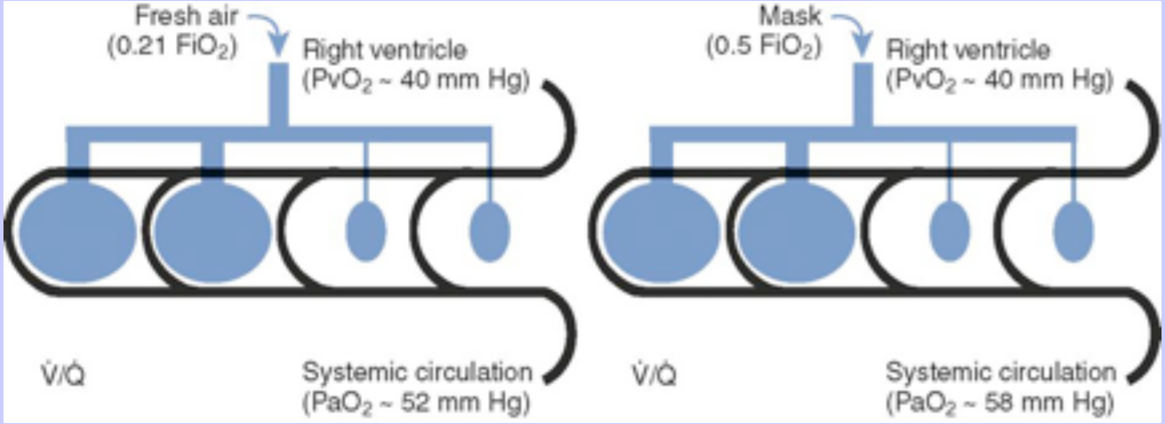


Figure 9-3 In the diagram on the left, the right two lung units have collapsed and are not ventilated. Blood still flows past them, resulting in a shunt. The diagram on the right depicts the same lungs with a higher fraction of inspired oxygen from supplemental oxygen. The partial pressure of oxygen in arterial blood increases minimally (58 mm Hg compared with 52 mm Hg); the patient is still hypoxemic.



Shunt occurs when venous blood bypasses gas exchange areas of the lung and mixes with oxygenated arterial blood. The venous admixture can result from either cardiac or pulmonary shunt. Examples of cardiac shunt include

Eisenmenger's ventricular septal defect and tetralogy of Fallot. Pulmonary shunt can result from pulmonary masses, complete lung atelectasis, or pulmonary disease causing regions of alveolar collapse and/or obstruction. Shunt is the most important cause of clinically significant hypoxemia, because it is not very responsive to oxygen therapy (Figure 9-3). This is because the oxygen content of the blood perfusing the ventilated alveoli can be increased only minimally with an increased FiO_2 and is insufficient to compensate for the very low oxygen content of the blood perfusing the unventilated alveoli.[1,5]

Diffusion impairment implies that normal equilibration between alveolar gas and pulmonary capillary blood does not occur. Diffusion of oxygen across the alveolar-arterial membrane depends on the concentration difference of oxygen across the membrane and the surface area and thickness of the gas exchange membrane.

In a resting animal, a red blood cell spends ¾ of a second in the pulmonary capillary. Normally the PO_2 of the capillary blood approaches that of the alveolar gas in one third of that time. Strenuous exercise may decrease transit time, but because of the ½-second reserve, normal equilibration can occur. Some diseases and conditions (smoke inhalation, oxygen toxicity) can cause thickening of the blood-gas interface, slowing diffusion to the point that equilibration is incomplete. Hypoxemia caused by diffusion impairment can be corrected by administering supplemental oxygen to the patient, raising the concentration difference.

Carbon dioxide is 20 times more soluble than oxygen. For this reason carbon dioxide retention is not usually a problem with diffusion impairment. PCO_2 is often lower in these patients, because they hyperventilate in an attempt to reverse the hypoxemia. Pulmonary diseases that decrease the area of gas exchange or increase the thickness of the alveolar-arterial membrane can cause impaired gas exchange. Examples of such diseases include pulmonary interstitial fibrosis and chronic emphysema.[4,5]

If gas exchange is impaired, some insight into the responsible mechanism can be gained by noting the response to breathing 100% oxygen. If hypoxemia is caused by hypoventilation or diffusion impairment, oxygen supplementation will rapidly and objectively correct the hypoxemia. If there is no response to supplemental oxygen, then shunt is the most likely mechanism of impaired gas exchange. Low V_A/Q also should be responsive to supplemental oxygen. Clinically however, whenever low V_A/Q is present, pulmonary shunt is almost always also present, so often only a partial response to supplemental oxygen is observed.

9.8 CONCLUSION

Tachypnea may occur with or without concurrent hypoxemia. Evaluation of oxygenation status is essential in the tachypneic patient, because hypoxemia necessitates rapid therapeutic and diagnostic interventions. With an understanding of the work of breathing and the mechanisms of hypoxemia, the critical care clinician can gain insight into the reasons for tachypnea and hypoxemia in the critically ill patient. An obstructive breathing pattern can help bring focus on causes of airway obstruction, and a restrictive breathing pattern should draw our attention to intrathoracic pulmonary parenchymal diseases.

9.9 SUGGESTED FURTHER READING*

JA Lee, KJ Drobat: Respiratory distress and cyanosis in dogs. In LG King (Ed.): *Textbook of respiratory disease in dogs and cats*. 2004, Saunders, St Louis, *A detailed resource outlining the triage and treatment of hypoxemia in the dog.*

AB Lumb: In *Nunn's applied respiratory physiology*. ed 6, 2005, Butterworth Heinemann, Boston, *More detail than West's Physiology although harder to read. Another essential textbook for anyone with an interest in pulmonary disease*.

DC Mandell: Respiratory distress in cats. In LG King (Ed.): *Textbook of respiratory disease in dogs and cats*. 2004, Saunders, St Louis, *Like the previous reference, an excellent resource. Provides useful, detailed, approaches to the common problems encountered with tachypneic hypoxemic cats*.

D Sisson, SJ Ettinger: The physical examination. In PR Fox, D Sisson, N Moise (Eds.): *Textbook of canine and feline cardiology*. 1999, Saunders, Philadelphia, *An excellent review of the physical examination in dogs and cats. An excellent focus on the examination of cardiac and pulmonary systems*.

JB West: In *Respiratory physiology: The essentials*. ed 8, 2008, Lippincott Williams & Wilkins, Philadelphia, *Along with West's pulmonary pathophysiology: the essentials, two of the most complete yet understandable reviews of normal and abnormal respiratory physiology. Essential reading for emergency and critical care residents or anyone looking for a complete review of the respiratory system. A new, combined, edition expected in 2007*.

* See the CD-ROM for a complete list of references

10 Chapter 10 Shock

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10.1 KEY POINTS

- Shock is defined as inadequate cellular energy production and most commonly occurs secondary to poor tissue perfusion from low or unevenly distributed blood flow. This leads to a critical decrease in oxygen delivery (DO_2) compared to oxygen consumption (VO_2) in the tissues.
- There are numerous ways to classify shock, and many patients suffer from more than one type of shock simultaneously. A common classification scheme includes hypovolemic, distributive, and cardiogenic causes.
- For all forms of shock except cardiogenic shock, the mainstay of therapy involves rapid vascular access and administration of large volumes of isotonic crystalloid fluids. Studies have not shown a clear benefit of one type of fluid over another; however, failure to administer an adequate volume of fluids may contribute significantly to mortality.
- End points of resuscitation such as normalization of heart rate and blood pressure, improved pulse quality, and resolution of lactic acidosis are necessary to tailor therapy to the individual patient.
- Oxygen therapy and avoidance of stress are key components to the treatment of cardiogenic shock. Sedation and intubation may be required in dyspneic patients who fail to respond to diuretic therapy.

10.2 INTRODUCTION

Shock is defined as inadequate cellular energy production. It most commonly occurs secondary to poor tissue perfusion from low or unevenly distributed blood flow that causes a critical decrease in oxygen delivery (DO_2) in relation to oxygen consumption (VO_2). Although metabolic disturbances (e.g., cytopathic hypoxia, hypoglycemia, toxic exposures) and hypoxemia (e.g., severe anemia, pulmonary dysfunction, methemoglobinemia) can lead to shock, it most commonly results from a reduction in DO_2 secondary to one of three major mechanisms: loss of intravascular volume (hypovolemic shock), maldistribution of vascular volume (distributive shock), or failure of the cardiac pump (cardiogenic shock). Box 10-1 lists all of the functional classes of shock. An index of suspicion based on signalment and a brief history may help differentiate between these various causes of shock. Early recognition of cardiovascular instability, along with a combination of physical examination findings and point of care testing suggestive of reduced perfusion are all that is necessary to initiate therapy. Rapid, aggressive therapy and appropriate monitoring, along with the removal of any underlying causes, are necessary to optimize the chance for a successful outcome.

10.3 CLINICAL PRESENTATION

Hypovolemic shock is commonly associated with internal or external blood loss, or excessive loss of other body fluids (severe vomiting, diarrhea, polyuria, burns). In hypovolemic states, reduced cardiac output due to diminished venous return triggers compensatory mechanisms that attempt to raise the circulating blood volume. An increase in

sympathetic activity causes vasoconstriction, increased cardiac contractility, and tachycardia with a resultant rise in cardiac output. Extreme vasoconstriction and microvasculature alterations induce mobilization of fluid from the interstitial and extracellular spaces to the intravascular space. Additionally, a reduction in renal blood flow activates the renin-angiotensin-aldosterone system, which further upregulates the sympathetic nervous system and causes sodium and water retention via the production of both aldosterone and antidiuretic hormone, respectively. Since the net effect of these responses is to increase intravascular volume, clinical signs of shock may be subtle initially, characterized by mild to moderate mental depression, tachycardia with normal or prolonged capillary refill time, cool extremities, tachypnea, and a normal blood pressure. Pulse quality is often normal, and this stage is generally referred to as "compensated shock." With ongoing compromise of systemic perfusion, compensatory mechanisms 41
are inadequate and often begin to fail. Pale mucous membranes, poor peripheral pulse quality, depressed mentation, 42
and a drop in blood pressure become apparent as the animal progresses to decompensated shock. Ultimately, reduced organ perfusion results in signs of end organ failure (e.g., oliguria) and ultimately death.

10.3.1

Box 10-1 Functional Classifications and Examples of Shock

Hypovolemic: A decrease in circulating blood volume

Hemorrhage

Severe dehydration

Trauma

Cardiogenic: A decrease in forward flow from the heart

Congestive heart failure

Cardiac arrhythmia

Cardiac tamponade

Drug overdose (anesthetics, β-blockers, calcium channel blockers, etc.)

Distributive: A loss of systemic vascular resistance

Sepsis

Obstruction (heartworm disease, saddle thrombosis)

Anaphylaxis

Metabolic: Deranged cellular metabolic machinery

Hypoglycemia

Cyanide toxicity

Mitochondrial dysfunction

Cytopathic hypoxia of sepsis

Hypoxemic: A decrease in oxygen content in arterial blood

Anemia

Severe pulmonary disease

Carbon monoxide toxicity

Methemoglobinemia

Rather than causing an absolute reduction in circulating blood volume/hypovolemia, diseases such as sepsis and gastric dilatation and volvulus lead to maldistribution of blood flow and result in distributive shock. Dogs with sepsis or a systemic inflammatory response syndrome (SIRS) can show clinical signs of hyperdynamic or hypodynamic shock (seeChapters 11 and 107, Systemic Inflammatory Response Syndrome and Septic Shock, respectively). The initial hyperdynamic phase of sepsis or SIRS is characterized by tachycardia, fever, bounding peripheral pulse quality and hyperemic mucous membranes secondary to cytokine (e.g., nitric oxide)-mediated peripheral vasodilatation. This is often referred to as vasodilatory shock. If septic shock or SIRS progresses unchecked, a decreased cardiac output and signs of hypoperfusion often ensue due to cytokine effects on the myocardium or myocardial ischemia. Clinical changes may then include tachycardia, pale (and possibly icteric) mucous membranes with a prolonged capillary refill time, hypothermia, poor pulse quality, and a dull mentation. Hypodynamic septic shock is the decompensatory stage of sepsis, and without intervention will result in organ damage and death. Lastly, the gastrointestinal tract is the shock organ in dogs, so shock often leads to ileus, diarrhea, or melena.

The hyperdynamic phase of shock is rarely recognized in cats. Also, in contrast to dogs, changes in heart rate in cats with shock are unpredictable; they may exhibit tachycardia or bradycardia. In general, cats typically present with pale mucous membranes (and possibly icterus), weak pulses, cool extremities, hypothermia, and generalized weakness or collapse. In cats, the lungs seem to be the organ most vulnerable to damage during shock or sepsis and signs of respiratory dysfunction are common.[1-3]

Dogs with gastric dilatation-volvulus may have normal circulating blood volume; however, compression of the major vessels secondary to severe gastric dilatation causes decreased venous return and reduced cardiac output. This is a form of relative hypovolemia. Although the classifications of shock are useful in understanding the underlying mechanism of cardiovascular instability, it is important to remember that different forms of shock can occur simultaneously in the same patient. A dog with gastric dilatation-volvulus, for example, will often have a component of hypovolemic shock secondary to blood loss associated with rupture of the short gastric vessels. Dogs with septic peritonitis may experience tissue hypoxia due to reduced of systemic vascular resistance, but likely suffer from hypovolemia as well if severe cavitary effusions or protracted vomiting are present.

10.4 DIAGNOSTICS AND MONITORING

There are some basic diagnostic tests that should be completed for all shock patients in order to assess the extent of organ injury and identify the etiology of the shock state. A venous or arterial blood gas with lactate measurement, a complete blood cell count, blood chemistry panel, coagulation panel, blood typing, and urine analysis should be performed. Thoracic and abdominal radiographs, abdominal ultrasound, and echocardiography may be indicated once the patient is stabilized.

Additional monitoring techniques that are essential in the diagnosis and treatment of the shock patient include continuous ECG monitoring, blood pressure measurement, and pulse oximetry (see Monitoring section). Gradual resolution of tachycardia often signals successful return of cardiovascular stability, whereas persistent tachycardia indicates ongoing cardiovascular instability. It is important to note that the best form of monitoring is a thorough physical examination, and frequent patient assessment will also provide important clues regarding response to therapy.

10.4.1 Monitoring Tissue Perfusion and Oxygen Delivery

The magnitude of the oxygen deficit is a key predictor of outcome in shock patients. Therefore optimizing oxygen delivery and tissue perfusion is the goal of treatment and sufficient monitoring tools are necessary to achieve this objective. A well-perfused patient possesses the following characteristics: central venous pressure between 5 and 10 cm H_2O (2 to 5 cm H_2O in cats); urine production of at least 1 ml/kg/hr; mean arterial pressure between 70 and 120 mm Hg; normal body temperature, heart rate, heart rhythm, and respiratory rate; and moist, pink mucous membranes with a capillary refill time of less than 2 seconds. Monitoring these parameters is the tenet of patient assessment. Additional monitoring tools that may prove beneficial include the measurement of blood lactate, indices of systemic oxygenation transport, and mixed venous oxygen saturation.

10.4.2 Blood Lactate Levels

Critically ill patients with inadequate oxygen delivery, oxygen uptake, or tissue perfusion often develop a hyperlactatemia and acidemia that are reflective of the severity of cellular hypoxia. A lactic acidosis in human patients carries a greater risk for developing multiple organ failure, and these people demonstrate a higher mortality rate than those without an elevated lactate concentration.[4] High blood lactate levels may also aid in predicting mortality in dogs.[5-7] The normal lactate concentration in adult dogs and cats is less than 2.5 mmol/L; lactate concentrations greater than 7 mmol/L are severely elevated.[5] However, normal neonatal and pediatric patients may have higher lactate concentrations.[8] In addition, sample collection and handling procedures can affect lactate concentration.[9] Serial lactate measurements taken during the resuscitation period help to gauge response to treatment and to evaluate resuscitation end points; the changes in lactate concentrations are a better predictor of survival than are single measurements.

10.4.3 Cardiac Output Monitoring and Indices of Oxygen Transport

The measurement of indices of systemic oxygen transport is a direct method of assessing the progress of resuscitation in shock patients. A right-sided cardiac catheter or pulmonary artery catheter (PAC, also termed Swan-Ganz catheter or balloon-directed thermodilution catheter) is typically used to monitor these parameters 42
(see Chapter 50, Pulmonary Artery Catheterization). The PAC enables the measurement of central venous and 43
pulmonary arterial pressure, mixed venous blood gases (PvO_2 and SvO_2), pulmonary capillary wedge pressure (PCWP), and cardiac output. With this information, further parameters of circulatory and respiratory function can be derived (i.e., stroke volume, end-diastolic volume, systemic vascular resistance index, pulmonary vascular resistance index, arterial oxygen content, mixed-venous oxygen content, DO_2 index, VO_2 index and the oxygen extraction ratio). Although cardiac output is typically determined using thermodilution methods, other techniques are available (see Chapter 203, Hemodynamic Monitoring).

A PAC allows the clinician to assess the cardiovascular and pulmonary function of shock patients. The response to treatment and titration of fluid therapy, vasopressors, and inotropic agents can also be monitored. Cardiac output and systemic DO_2 should be optimized using intravascular volume loading until the PCWP approaches 10 to 12 mm Hg. A high PCWP (>15 to 20 mm Hg) will promote the formation of pulmonary edema, further impairing oxygenation and overall oxygen transport. Despite potential benefits, the use of a PAC does not necessarily translate into reduced mortality in the critically ill shock patient; it is an invasive monitoring technique that is not without risk.[10] In addition, the accuracy of measurements provided by the PAC relies on catheter placement, calibration of transducers, coexisting cardiac or pericardial disease, and correct interpretation of waveforms and values.

10.4.4 Mixed Venous Oxygen Saturation (SvO_2) and Central Venous Oxygen Saturation ($ScvO_2$)

Changes in the global tissue oxygenation (oxygen supply-to-demand) can be assessed using SvO_2 measurements. Assuming VO_2 is constant, SvO_2 is determined by cardiac output, hemoglobin concentration, and SaO_2. SvO_2 is decreased if DO_2 decreases (low CO, hypoxia, severe anemia) or if VO_2 increases (fever). With conditions such as the hyperdynamic stages of sepsis and cytotoxic tissue hypoxia (e.g., cyanide poisoning), SvO_2 is increased. A reduction in SvO_2 may be an early indicator that the patient's clinical condition is deteriorating. In addition, SvO_2 may be an alternative to measuring cardiac index during resuscitative efforts.

Ideally, SvO_2 is measured in a blood sample from the pulmonary artery. However, in animals that do not have a PAC, venous oxygen saturation can be measured from the central circulation, using a central venous catheter in the cranial vena cava. SvO_2 is then termed $ScvO_2$ (central venous oxygen saturation). Although the $ScvO_2$ values are generally higher than SvO_2 in critically ill patients with circulatory failure, the two measurements closely parallel one another. Therefore a pathologically low $ScvO_2$ likely indicates an even lower SvO_2. A recent prospective, randomized study comparing two algorithms for early goal-directed therapy in patients with severe sepsis and septic shock showed that maintenance of a continuously measured $ScvO_2$ above 70% (in addition to maintaining central venous pressure above 8 to 12 mm Hg, [MAP] pressure above 65 mm Hg, and urine output above 0.5 ml/kg/hr) resulted in a 15% absolute reduction in mortality compared to the same treatment without $ScvO_2$ monitoring.[11] Though it is not clear if these exact parameters can be readily applied to veterinary patients, early recognition of shock followed by aggressive goal driven resuscitation is likely crucial to successful treatment of shock.

10.5 TREATMENT

Treatment of shock is based on early recognition of the condition and rapid restoration of the cardiovascular system so that DO_2 to the tissues is normalized as soon as possible. The mainstay of therapy for all forms of shock except that of shock of cardiogenic origin is based on rapid administration of large volumes of intravenous fluids to restore an effective circulating volume and tissue perfusion. Vascular access is essential for successful treatment of shock, but can be difficult due to poor vascular filling and a collapsed cardiovascular state. Since speed of fluid administration is proportional to the diameter of the catheter lumen and inversely proportional to its length, short, large-bore catheters should be placed in a central or peripheral vein. In cases in which intravenous access is difficult or delayed due to cardiovascular collapse, a cut-down approach or intraosseous catheterization may be necessary (see Chapters 61 to 63, Peripheral Venous Catheterization, Intraosseous Catheterization, and Central Venous Catheterization, respectively).

The type of fluid selected for the treatment of shock may vary (see Chapter 65, Shock Fluids and Fluid Challenge). Replacement isotonic crystalloids such as lactated Ringer's solution, 0.9% sodium chloride (NaCl), or Normosol R form the mainstay of therapy for shock, administered rapidly at doses equivalent to 1 blood volume (90 ml/kg for the dog, 40 to 60 ml/kg for the cat). The administered fluid rapidly distributes into the extracellular fluid compartment so that only approximately 25% of the delivered volume remains in the intravascular space by 30 minutes after infusion,[12] and some animals will therefore require additional resuscitation at this time point. In patients that are bleeding, it may even be advantageous to perform hypotensive resuscitation (to an MAP of ~60 mm Hg) until the hemorrhage is controlled, because aggressive fluid therapy in this setting can worsen bleeding and outcome.[13] For animals with coexisting head trauma, the isotonic crystalloid of choice is 0.9% NaCl because it contains the highest concentration of sodium and is least likely to contribute to cerebral edema. The “shock doses” of crystalloids serve as useful guidelines for fluid resuscitation of the shock patient; however, the actual volume administered should be titrated according to the patient's clinical response in order to prevent volume overload. Excessive fluid administration is often evidenced by pulmonary or peripheral edema due to any combination of increased hydrostatic pressure, hypoalbuminemia, and increases in vascular endothelial permeability. Animals with uncontrolled hemorrhage or deranged compensatory mechanisms may not respond adequately to crystalloid resuscitation and will require additional therapeutic, diagnostic, and monitoring strategies. Additional fluid therapy options in these patients include synthetic colloid solutions, hypertonic saline, blood products, and hemoglobin-based oxygen carrying (HBOC) solutions.

Synthetic colloids such as hetastarch or dextran 70 are hyperoncotic to the normal animal and therefore pull fluid into the vascular space following intravenous administration. They therefore cause an increase in blood volume that is greater than that of the infused volume and help to retain this fluid in the intravascular space in animals with 43
normal capillary permeability. They are appropriately used for shock therapy in acutely hypoproteinemic animals 44
(total protein <3.5 g/dl) with a decreased colloid osmotic pressure. They can also be used with isotonic or hypertonic crystalloids to maintain adequate plasma volume expansion with lower interstitial fluid volume expansion and to expand the intravascular space with smaller volumes over a shorter time period. Due to the prevalence of occult cardiac disease in cats, hetastarch or dextran-70 is typically administered more conservatively in this species, at doses ranging from 5 to 10 ml/kg compared to 10 to 20 ml/kg in dogs. With the exception of human trauma patients, studies have failed to support a survival benefit with the use of colloids compared to crystalloids in resuscitation

from shock. In the specific population of human trauma patients, crystalloid use has been associated with reduced mortality compared to colloid therapy.[14] Human albumin, a natural, hyperoncotic and hyperosmotic colloid solution with rising popularity in veterinary medicine, is another therapeutic option when crystalloid therapy alone has failed to restore or maintain an effective circulating blood volume. Preliminary studies in dogs found that albumin therapy increases circulating albumin concentrations, total solids, and colloid osmotic pressure, although the effect on mortality remains unknown. Potential complications are reportedly rare in critically ill animals and are similar to those for any blood product transfusion (i.e., fever, vomiting, increased respiratory effort), in addition to the potential for increasing clotting times. However, few studies have been published evaluating the safety of human albumin in animals. Recent reports of albumin administration to normal research dogs revealed potentially fatal reactions to the product, especially with repeated dosing.[15] Caution is therefore advised at this time.

The use of 7% to 7.5% sodium chloride (hypertonic saline) can be lifesaving in the emergency setting. The long shelf life and affordability of this solution render it a necessity in the veterinary emergency hospital. Following administration of hypertonic saline, there is a transient (<30 minutes) osmotic shift of water from the extravascular to the intravascular compartment. It is administered in small volumes (5 ml/kg) intravenously over 5 to 10 minutes. In addition to the fluid shift caused by hypertonic saline, there is evidence that it also helps to reduce endothelial swelling, modulates inflammation, increases cardiac contractility, causes mild peripheral vasodilation, and decreases intracranial pressure. The effects of this solution are immediate, with a decrease in heart rate and improvement of pulse quality typically noted within 1 to 2 minutes of administration. Though short-lived, this transient improvement in cardiovascular state may provide the necessary time for other therapies to take effect. Hypertonic saline should always be used in combination with other resuscitative fluids due to the osmotic diuresis and rapid sodium redistribution that occur following administration. A mixture of hypertonic saline and a synthetic colloid may further augment and prolong the rise in blood volume compared to hypertonic saline alone. Several studies in dogs suggest that the combination of hypertonic saline and dextran-70 is associated with more rapid improvement in hemodynamic status and with lesser overall crystalloid requirements than when crystalloids are used alone.[16,17]

Blood component therapy is frequently used during resuscitation of the shock patient. Most fluid-responsive shock patients will tolerate acute hemodilution to a hematocrit of less than 20%. In the dog, splenic contraction secondary to catecholamine release may mask the presence of anemia, and a reduced total protein concentration can be used to raise the index of suspicion for blood loss in this species. Both the dose of packed red blood cells and speed of administration may vary depending on the underlying condition and the hemodynamic state of the patient. In animals with acute blood loss that are unresponsive to fluid therapy alone, fresh whole blood or packed red blood cells and fresh frozen plasma should be used in an attempt to stabilize clinical signs of shock and maintain the hematocrit above 25% and the clotting times within the normal range (see Chapter 66, Transfusion Medicine). Packed red blood cells and fresh frozen plasma are administered at a dose of 10 to 15 ml/kg and fresh whole blood at a dose of 20 to 25 ml/kg. Although all blood products should be administered over at least 1 to 2 hours in order to monitor for a transfusion reaction and avoid volume overload, it may be necessary to administer these products in bolus doses in animals with severe internal or external blood loss. A blood type should be determined in all animals, especially cats, before transfusions are given. Packed red blood cells are given to increase oxygen content in animals with severe anemia or in conjunction with fresh frozen plasma in coagulopathic shock patients. Plasma products are most commonly used in animals with profound blood loss, a coagulopathy, or severe hypoalbuminemia (large volumes of intravenous fluids in a short period of time may also have a dilutional effect on circulating coagulation factors). Its ability to increase colloid osmotic pressure is limited compared to the hyperoncotic synthetic colloids, but it does supply albumin, an important carrier of certain drugs, hormones, metals, chemicals, toxins, and enzymes. Platelets are only present in fresh blood within 24 hours of collection and their use is indicated in animals with thrombocytopenia/thrombocytopathia-induced bleeding disorders or massive hemorrhage.

Finally, HBOC solutions may be beneficial for the treatment of shock. In states of anemia, the HBOC solutions may increase oxygen delivery to tissues and increase perfusion of capillary beds affected by microvascular thrombosis due to the small size of the free hemoglobin. Despite these theoretical benefits and the long shelf life of this product, HBOC solutions are not widely used due to inconsistent supply, undesirable side effects and lack of clear benefit over other solutions available.

Shock patients that remain hypotensive despite intravascular volume resuscitation often require vasopressor and/or inotrope therapy. Because oxygen delivery to the tissue is dependent on both cardiac output and systemic vascular resistance, therapy for hypotensive patients includes maximizing cardiac output with fluid therapy as discussed above and inotropic drugs and/or modifying vascular tone with vasopressor agents (see Chapters 6, 176, and 177, Hypotension, Vasoactive Catecholamines, and Vasopressin, respectively). Commonly used vasopressors include catecholamines (epinephrine, norepinephrine, dopamine) and the sympathomimetic drug phenylephrine. In addition, vasopressin, corticosteroids, and glucagon have been used as adjunctive pressor agents.

Unlike hypovolemic or distributive shock, cardiogenic shock is characterized by a systolic or diastolic cardiac dysfunction resulting in hemodynamic abnormalities such as increased heart rate, decreased stroke volume, 44 decreased cardiac output, decreased blood pressure, increased peripheral vascular resistance, and increases in the 45 right atrial, pulmonary arterial, and pulmonary capillary wedge pressures (see Chapter 35, Cardiogenic Shock). These pathologic changes result in diminished tissue perfusion and increased pulmonary venous pressures, resulting in pulmonary edema and dyspnea. Supplemental oxygen therapy and minimal handling are extremely important to avoid further decompensation in patients with cardiogenic shock. A brief physical examination consisting of thoracic auscultation alone may identify the presence of a cardiac murmur or gallop rhythm and pulmonary crackles. In cats, hypothermia may be very helpful in differentiating heart failure from other causes of dyspnea.

Successful treatment of cardiogenic shock depends on rapid evaluation of signalment, a brief physical examination, and avoidance of stress. The diuretic furosemide (2 to 8 mg/kg) administered intravenously or intramuscularly is that mainstay of therapy for congestive heart failure. Animals that fail to show clinical signs of improvement following repeated doses of diuretics may require more specific therapy targeting the underlying cardiac abnormality (e.g., systolic dysfunction, diastolic failure, arrhythmias). Ultimately, the dyspneic patient in cardiogenic shock that fails to respond to therapy should be anesthetized, intubated, and positive pressure ventilated with 100% oxygen to stabilize the animal, remove the anxiety associated with shortness of breath, and allow the clinician to perform a thorough physical examination and pursue further diagnostics such as thoracic radiographs and echocardiography.

Early recognition and initiation of therapy are essential for successful treatment of the shock patient. Therapy for the shock patient is complicated by the need for rapid decision-making in the absence of a complete medical history. In all forms of shock other than cardiogenic shock, intravenous fluid administration is the mainstay of therapy. Although underresuscitation or delayed onset of therapy could clearly contribute to a negative outcome, excessive or overaggressive resuscitation may also have undesirable consequences, including a dilutional coagulopathy and pulmonary edema. The combination of breed, signalment, and physical examination findings will help the emergency clinician identify the type of shock present, and serial evaluation with clearly defined end points of resuscitation are essential for successful management of the shock patient.

10.6 SUGGESTED FURTHER READING*

A Boag, D Hughes: Assessment and treatment of perfusion abnormalities in the emergency patient. *Vet Clin North Am Small Anim Pract*. **35**, 2005, 319, *A good discussion on the clinical signs and therapeutic approach to hypoperfusion.*

PT Choi, G Yip, LG Quinonez, et al.: Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med*. **27**, 1999, 200, *This review examined all randomized clinical trials of adult humans requiring fluid resuscitation that compared crystalloid to colloid therapy. No difference in development of pulmonary edema, mortality or length of stay was identified, however reduced mortality was seen in trauma patients receiving isotonic crystalloids*.

E Rivers, B Nguyen, S Havstad, et al.: Early goal directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. **345**, 2001, 1368, A landmark study that found patients with severe sepsis or septic shock assigned to receive early goal directed therapy from 7 to 72 hours after admission had a significantly higher mean central venous oxygen saturation, lower lactate concentration, lower base deficit, higher pH, and less severe organ dysfunction than the patients assigned to standard therapy.

DC Silverstein, J Aldrich, SC Haskins, et al.: Assessment of changes in blood volume in response to resuscitative fluid administration in dog. *J Vet Emerg Crit Care*. **15**, 2005, 185, *An experimental study in four healthy dogs showing that the rapid administration of saline at clinically relevant doses leads to the largest immediate increase in blood volume. Hypertonic saline led to the smallest increase in blood volume post-infusion and the synthetic colloid solutions increased the blood volume for a longer period of time than the other fluids*.

RW Taylor: Pulmonary Artery Consensus Conference Participants: Consensus statement. *Crit Care Med*. **25**, 1997, 910, *The experts in the field recognize that the PAC may be useful in shock unresponsive to fluid resuscitation and vasopressors though it is not clear whether the PAC is superior to other, less invasive forms of monitoring*.

[*] See the CD-ROM for a complete list of references.

11 Chapter 11 Systemic Inflammatory Response Syndrome

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11.1 Key Points

- Systemic inflammatory response syndrome (SIRS) is a widespread response to an infectious or a noninfectious insult and, if left untreated, can lead to multiple organ failure and death.
- Under normal conditions, the release of proinflammatory mediators and acute phase proteins triggers a compensatory antiinflammatory response that leads to restoration of a homeostatic state.
- Criteria used to identify SIRS are nonspecific and may lead to over-diagnosis of this condition.
- Severe systemic inflammation often leads to vascular hyporesponsiveness, increased endothelial permeability, and a hypercoagulable state.
- Treatment of SIRS consists of supportive care and treatment of the underlying disease.

11.2 INTRODUCTION

Systemic inflammatory response syndrome (SIRS) is a term introduced by the American College of Chest Physicians and Society of Critical Care Medicine consensus conference in 1992 to acknowledge the importance of systemic activation of inflammation as a contributor to organ failure in sepsis.[1] The inherent heterogeneity of patients with sepsis and the observation of similar clinical courses in disease states lacking an infectious cause led to the breakdown of sepsis into a trigger (bacterial invasion) and a response to that trigger (the inflammatory response). From this realization emerged the concept of SIRS, or a systemic response to an insult that is infectious or noninfectious in origin.

Although SIRS is most commonly associated with sepsis, other disease states known to cause widespread release of endogenous mediators and subsequent systemic inflammation in people include trauma, burns, major surgery, and pancreatitis.[2] These insults can progress to multiple organ failure, shock, and death due to the magnitude of the inflammatory response alone (and in the absence of infection).[2,3] SIRS describes a clinical state rather than a disease entity. Proposed criteria for diagnosis consist of two out of the following four clinical signs: (1) hypothermia or hyperthermia, (2) leukocytosis or leukopenia, (3) tachycardia, and (4) tachypnea.[1] Studies relating the magnitude of the inflammatory response to outcome highlight the importance of early recognition of systemic inflammation and treatment of the underlying disease process.[4]

11.3 SYSTEMIC INFLAMMATION

Systemic inflammation may be triggered by products of both gram-positive and gram-negative bacteria. Factors known to stimulate macrophages and monocytes include lipopolysaccharide (from gram-negative bacteria), lipoteichoic acid (gram-positive bacteria), peptidoglycan and flagellin (gram-positive and gram-negative bacteria), and mannan (fungi). Normally leukocyte activation resulting from exposure to these proteins, and subsequent release of tumor necrosis factor-α (TNF-α), lead to an inflammatory response designed to protect the host. Excessive activation of inflammation, however, may contribute to multiple organ failure and death.

Although the release of mediators such as TNF-α, interleukin (IL)-1, IL-6, prekallikreins, bradykinin, platelet activating factor, and others in response to leukocyte activation has been well characterized, this proinflammatory response is accompanied by activation of antiinflammatory measures designed to counteract the proinflammatory state. This compensatory antiinflammatory response syndrome (CARS) is characterized by the release of antiinflammatory mediators, including IL-10, transforming growth factor-β (TGF-β), and IL-13; production of soluble receptors and receptor antagonists for cytokines such as TNF-α; and reduction of B and T lymphocyte production. Although clearly beneficial in its ability to control the proinflammatory state, excessive stimulation of the compensatory antiinflammatory response may contribute to immunoparalysis and increased susceptibility to nosocomial infections seen in the late stages of sepsis.[5-7]

11.4 CONSEQUENCES OF SYSTEMIC INFLAMMATION

Disruptions in homeostasis caused by production of proinflammatory mediators include loss of vascular tone, disruption of the endothelial permeability barrier, and stimulation of coagulation (see Chapter 107, Septic Shock). Loss of vascular tone is thought to occur secondary to excessive inducible nitric oxide synthase (iNOS) production, the precursor to nitric oxide release, and possibly a deficiency of vasopressin (a potent vasoconstrictor hormone). Disruption of the endothelial permeability barrier is a direct result of cytokine production.[8,9]

A hypercoagulable state, induced by cytokine-mediated tissue factor expression on the surface of leukocytes, leads to fibrin deposition in the microvasculature and is thought to contribute to organ failure in proinflammatory states. Endogenous anticoagulant systems such as antithrombin, protein C, and tissue factor pathway inhibitor are overwhelmed in states of systemic inflammation. Interestingly, studies have supported a close relationship between inflammation and coagulation.[10,11] Thrombin resulting from the activation of coagulation stimulates leukocyte activation and further cytokine production.

TNF-α downregulates the activation of protein C, which is known to have antiinflammatory properties in addition to its role as an anticoagulant. Administration of drotrecogin-α, or recombinant human activated protein C, significantly improved survival in humans with sepsis.[12] Studies suggest, however, that the beneficial effect of protein C may be due to its antiinflammatory effect rather than its anticoagulant properties.[13]

11.5 SIRS AND SEPSIS

Although SIRS has been identified as an important component of sepsis, it can occur in the absence of infection, yet have a clinical course resembling that of sepsis. Parameters such as body temperature, heart rate, and respiratory rate are useful to identify systemic inflammation, but they lack sensitivity and specificity for the diagnosis of sepsis. The time required to obtain culture results precludes their usefulness in differentiating nonseptic SIRS from septic SIRS in most clinical situations. This need to differentiate sepsis from SIRS of noninfectious origin has led to the search for biologic markers that would identify the presence (or lack of) bacterial infection in patients with clinical signs of SIRS. C-reactive protein (CRP) and procalcitonin (PCT) have both been studied extensively in humans. Additionally, use of the PIRO (predisposition, insult or infection, response, and organ dysfunction) acronym was adopted following the 2001 Sepsis Definitions conference to more accurately stage sepsis and describe the clinical manifestations of the infection and the host response (see Chapter 106, Sepsis).

11.6 MARKERS OF SEPSIS

CRP is an acute phase protein produced by hepatocytes in response to inflammatory cytokine release, including TNF-α and IL-1β. CRP release peaks 36 to 50 hours following secretion and it has a half-life of 19 hours. Although studies support a rise in CRP in humans with sepsis,[14] elevations have also been documented secondary to other inflammatory processes such as trauma, surgery, acute pancreatitis, and myocardial infarction.[15] Some studies have also suggested that CRP levels reflect the severity of the inflammatory process, but these levels have not been shown to differ between survivors and nonsurvivors.[16] Because of the prolonged half-life and lack of specificity, CRP is not considered the ideal marker for the diagnosis of sepsis.

PCT, the precursor molecule to calcitonin, has also been investigated as a potential marker of sepsis. Normally produced by the thyroid gland, PCT during sepsis is thought to originate from mononuclear leukocytes following endotoxin and cytokine stimulation.[17] PCT is released hours after endotoxin release, and peak levels persist for up to 24 hours. Although the exact role of PCT in sepsis is still unknown, it is known to increase iNOS–mediated nitric oxide release and therefore may play a role in amplification of the inflammation.[18]

Studies have documented elevated PCT levels in bacterial infections complicated by systemic inflammation and little to no change in PCT in localized infections or in infections of viral etiology. These findings support the use of PCT to differentiate between bacterial sepsis and SIRS of nonbacterial origin in humans.[19] In some studies, PCT levels correlate with disease severity and may have prognostic value for sepsis and septic shock. Overall, PCT is thought to represent a superior marker of sepsis than CRP in humans.

11.7 TREATMENT OF SIRS IN HUMANS

Because systemic inflammation is a critical component of sepsis, studies investigating the benefit of therapeutic interventions for sepsis have focused on modulation of the inflammatory response. Cytokine blockade, in particular, has been investigated extensively as a means to control inflammation, prevent end-organ damage, and improve survival in severe sepsis and septic shock. TNF-α blockade using TNF antibody administration failed to improve survival consistently in people with sepsis and was shown in some studies to have detrimental effects.[20,21] Similarly, the use of receptor antagonists to TNF, platelet activating factor, and IL-1 failed to improve 28-day survival in those with severe sepsis.[22,23]

The antiinflammatory benefits of ibuprofen were also studied in a prospective, randomized, double-blinded, placebo-controlled trial. A survival benefit was not shown in humans with sepsis.[24] High-dose glucocorticoids, commonly used before the 1990s, were often administered to control the inflammatory response. This practice was discontinued due to failure to increase survival and, in some studies, increased mortality.[25] Human intravenous immunoglobulin was shown to increase survival in a small study of humans with gram-negative sepsis.[26] The immune-modulating properties of statins, drugs commonly used to control cholesterol in humans, have led to studies investigating their effect in diseases known to be associated with systemic activation of inflammation. Their potential benefits in people with SIRS and sepsis have yet to be determined.[27] By far, the results of the PROWESS study, showing a survival benefit with recombinant human activated protein C in humans with severe sepsis and septic shock, have made the greatest impact on the treatment of sepsis.[12] Recombinant human activated protein C has received a grade B recommendation in the most recent Survival Sepsis Campaign in people, but veterinary studies are lacking.[28]

11.8 SIRS IN SMALL ANIMALS

Knowledge relating to SIRS in animals is based on studies of animal models of sepsis and related diseases, and studies investigating the inflammatory response in naturally occurring animal diseases are lacking. Historically, studies of sepsis have often included both dogs and cats; however, increasing evidence supports significant differences in the manifestation of systemic inflammation in these species.

Common causes of SIRS in animals include sepsis, heat-stroke, pancreatitis, immune disease, neoplasia, severe polytrauma, and burns. Criteria for SIRS have been extrapolated from human studies for dogs and cats, but few prospective studies have been performed to validate these criteria. In one study of 30 septic and 320 nonseptic dogs, criteria found to have the greatest sensitivity for the diagnosis of SIRS were determined and are listed in Table 11-1.[29]

In both animals and humans, the criteria used for identification of SIRS may lead to over-diagnosis of this condition. In cats, proposed criteria for SIRS were derived from a retrospective study in which severe sepsis was identified at necropsy. This study identified inappropriate (or relative) bradycardia (HR <140 beats/min) in 66% of cats with severe sepsis.[30] Although the criteria for SIRS that were proposed as a result of this study have yet to be validated prospectively, relative bradycardia was also identified in 16% of cats with septic peritonitis.[31] This finding supports the fundamental difference between cats and dogs in the hemodynamic response to systemic inflammation.

Several studies have been performed investigating the alterations in hemostasis in dogs with systemic inflammation. In one study, all 9 dogs with parvoviral enteritis had evidence of hypercoagulability based on results of thromboelastography and a reduction in measured antithrombin activity.[32] In another study examining dogs with naturally occurring sepsis, protein C and antithrombin activities were reduced significantly in dogs with sepsis compared with controls, also suggesting the predominance of hypercoagulability in this disease process.[33] Potential uses of markers of inflammation in animals with SIRS include the differentiation between infectious and noninfectious causes of systemic inflammation, as well as the determination of severity of disease and response to therapy.

CRP is the acute phase protein that has received the most attention in the veterinary literature to date. In one study of dogs with naturally occurring pancreatitis, serum CRP concentrations were elevated in all 16 dogs with acute pancreatitis compared with controls, and CRP concentration decreased in all dogs that were hospitalized for 5 days.[34] Increased CRP concentration has been documented in a variety of disease states including autoimmune hemolytic anemia, various neoplasias,[35] chronic valvular disease,[36] and other diseases known to cause acute inflammation. The usefulness of CRP measurements in differentiating infectious from noninfectious SIRS in animals with naturally disease has not yet been investigated.

Studies investigating inflammatory mediators in animals with naturally occurring disease are lacking. In one study examining dogs with parvoviral enteritis, 7 of 17 had measurable TNF activity.[37] Proinflammatory cytokines have also been documented in other disease states that are thought to have an inflammatory component (e.g., cranial cruciate rupture in the dog).[38]

Clinical manifestations of SIRS are often nonspecific and may vary depending on the underlying disease process. In general, signs of SIRS often resemble those of sepsis, and in most cases they are both are managed similarly. Loss of appetite and depression are reported frequently in animals experiencing systemic inflammation. In addition to the clinical signs listed in Table 11-1, animals may exhibit injected mucous membranes and bounding peripheral pulses, suggesting a compensated hyperdynamic state, or vomiting and diarrhea (especially if the problem is gastrointestinal in origin). A high index of suspicion for SIRS may also be based on CBC changes such as a neutrophilic leukocytosis, with or without a left shift, and toxic cytologic changes to the neutrophils. Alterations frequently found on the biochemistry panel include hyperglycemia or hypoglycemia, hypoalbuminemia, elevated alanine aminotransferase and aspartate aminotransferase and, in some cases, hyperbilirubinemia. Changes in blood glucose are thought to occur secondary to altered carbohydrate metabolism, with increased gluconeogenesis causing hyperglycemia in the early phase of infection and inflammation, and hypoglycemia occurring later in the disease process when glucose utilization exceeds production. Reduced albumin concentration occurs secondary to reduced manufacture by the liver in favor of production of acute phase proteins, and also to loss induced by changes in endothelial permeability. Liver enzyme concentrations likely are altered by changes in perfusion and decreased oxygen delivery to tissues. Finally, cholestasis may be the cause of elevated serum bilirubin, although it has also been suggested that immune-mediated hemolysis may play a role. Endotoxins can cause intrahepatic cholestasis and icterus as well.

Table 11-1 Proposed Criteria for the Diagnosis of SIRS in Dogs and Cats

	Dogs: 2/4 Changes Required	**Cats: 3/4 Changes Required**
Temperature (°F)	<100.6 or >102.6	<100 or >104
Heart rate (beats/min)	>120	<140 or >225
Respiratory rate (breaths/min)	>20	>40
WBC (×10^3); % bands	<6 or >16; >3%	>19 or <5

SIRS, Systemic inflammatory response syndrome; *WBC,* white blood cells. Proposed criteria for the diagnosis of SIRS include at least two (in dogs) or three (in cats) of the changes listed. Criteria described for dogs were found to have a sensitivity of 97% and a specificity of 64% for the diagnosis of SIRS.[48]

It is important to note that cats and dogs differ in their manifestation of SIRS, with cats more likely to experience hypotension, hypoglycemia, and hyperbilirubinemia than dogs. Ultimately, clinical manifestations of SIRS resemble those of sepsis, with the finding of infection ultimately necessary to differentiate these two conditions.

The mainstay of treatment for patients with SIRS consists of treatment of the underlying disease process and supportive care. If infection is found or suspected along with clinical signs of SIRS, then treatment for sepsis consisting of source control, antibiotic therapy, and cardiovascular support should be initiated. Although SIRS may not always be of infectious origin, antibiotics frequently are added when an infectious cause is suspected but no specific infection is diagnosed. Until culture results are available, antibiotic therapy should be broad-spectrum so that gram-positive, gram-negative, and anaerobic organisms are covered. Common combinations include a cephalosporin, enrofloxacin, and metronidazole, or ampicillin and enrofloxacin (see Chapters 106 and 194, Sepsis and Antibiotic Use in the Critical Care Patient, respectively).

Once culture and sensitivity results are available, antibiotic therapy should be tailored to target the identified pathogen. More aggressive antibiotic therapy may be warranted if a hospital-acquired infection is suspected. Intravenous therapy generally consists of replacement fluids such as lactated Ringer's solution or Normosol-R. Fluid therapy is aimed at resolving hypovolemia, maintaining daily requirements, and replacing any ongoing losses, and should be tailored to the individual patient (see Chapter 64, Daily Intravenous Fluid Therapy). It is important to note that inflammatory mediators associated with systemic inflammation also lead to changes in endothelial permeability;

therefore excessive crystalloid administration may result in interstitial fluid accumulation and clinical signs of peripheral edema.

Other therapies may include oxygen supplementation (see Chapter 19, Oxygen Therapy), nutritional support by enteral or parenteral routes (see Chapters 13 and 14, Enteral Nutrition and Parenteral Nutrition, respectively), and stress ulcer prophylaxis (see Chapter 181, Gastrointestinal Protectants).

Monitoring the patient with SIRS consists of regular evaluations of volume and perfusion status using repeated physical examinations, measurement of serum lactate concentrations, central venous pressure measurements, serial body weights, and comparison of intake to output. Intermittent blood pressure measurements may be helpful, and vasopressor therapy is indicated if fluid therapy alone fails to resolve hypotension (see Chapter 176, Vasoactive Catecholamines). The hematocrit and serum electrolyte, albumin, and glucose concentrations should be monitored regularly. Complications of SIRS include cardiovascular collapse, disseminated intravascular coagulation, and multiple organ dysfunction.

11.9 CONCLUSION

Systemic inflammation has received widespread attention as a key component of sepsis in both people and in animals. SIRS is classically associated with diseases such as pancreatitis and sepsis in dogs and cats, but may be underrecognized as a contributor to cardiovascular collapse and organ failure in animals with other diseases (i.e., polytrauma, neoplasia). Cats in particular may be more susceptible to noninfectious SIRS, a clinical state that often appears similar to that of sepsis and may result in organ failure and death.

Supportive care aimed at preserving organ function and treatment of the underlying disease process remain the mainstays of therapy. Low-dose glucocorticoid and intravenous immunoglobulin administration warrant further study in animals with naturally occurring disease.

11.10 SUGGESTED FURTHER READING*

AL Beal, FB Cerra: Multiple organ failure syndrome in the 1990s. Systemic inflammatory response and organ dysfunction. *J Am Med Assoc*. **271**, 1994, 226, *A nice straightforward review of the pathophysiology and treatment of SIRS that focuses on how the changes related to systemic inflammation lead to organ dysfunction.*

RC Bone, RA Balk, FB Cerra, et al.: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis, ACCP/SCCM Consensus Conference Committee. *Chest*. **101**, 1992, 1644, *A must-read for anyone with an interest in SIRS and sepsis to understand the basis for and definitions of these terms.*

MF Costello, KJ Drobatz, L Aronson, et al.: Underlying cause, pathophysiologic abnormalities, and response to treatment in cats with septic peritonitis: 51 cases (1990-2001). *J Am Vet Med Assoc*. **225**, 2004, 897–902, *A study that described physical examination and clinicopathologic findings in cats with septic peritonitis—relative bradycardia in cats with septic peritonitis being an important finding in support of this important difference between cats and dogs with sepsis.*

JG Hauptman, R Walshaw, NB Olivier: Evaluation of the sensitivity and specificity of diagnostic criteria for sepsis in dogs. *Vet Surg*. **26**, 1997, 393, *The only study to evaluate the sensitivity and specificity of SIRS criteria in dogs.*

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* See the CD-ROM for a complete list of references

12 Chapter 12 Nosocomial Infections and Zoonoses

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12.1 Key Points

- Nosocomial (hospital acquired) infection is defined as any infection that is neither present nor incubating when a patient is admitted to a hospital.
- Risk factors for nosocomial infection in the intensive care unit (ICU) include severity of underlying illness, prolonged length of stay, mechanical ventilation, and indwelling devices.
- Multiple antibiotic resistance is common among nosocomial pathogens.
- Methicillin-resistant *Staphylococcus aureus* is an emerging disease in dogs and cats.
- Zoonosis is a disease that can be transmitted from animals to humans. A more technical definition is a disease that normally exists in animals but that can infect humans.
- The reservoirs of nosocomial pathogens include people, animals, fomites, air currents, water and food sources, insects, and rodents, and it has long been known that the spread of pathogens in hospitals occurs primarily via the hands of personnel.
- Establishment of nosocomial infection control committees must become a priority in veterinary hospitals.

12.2 INTRODUCTION

In human health care settings, nosocomial infection is defined as any infection that is neither present nor incubating when a patient is admitted to a hospital. In 1988, the Centers for Disease Control and Prevention proposed more specific definitions, and it is now generally accepted that infections are considered to be nosocomial if they develop at least 48 hours after hospital admission without proven prior incubation.[1] In addition, if infections occur up to 3 days after discharge or within 30 days of a surgical procedure, they are attributed to the admitting hospital.[1] These definitionsare largely accepted in human health care and, although they may require refinement in veterinary medicine, they stand unchallenged.

It is well recognized that hospitalization of sick animals can lead to an increased risk of infection, and various policies have been proposed to reduce the risk of nosocomial infection in veterinary medicine.[2,3] In addition to patient care concerns, many nosocomial pathogens are well recognized as zoonotic agents, so infection control policies should address the issue of animal to human transmission.[2]

12.3 NOSOCOMIAL INFECTIONS IN DOGS AND CATS

One of the first published reports of nosocomial infection in a veterinary hospital described *Klebsiella* infection in dogs and one cat in the ICU at the New York State College of Veterinary Medicine in 1978.[4] Since that time there have been a few well-characterized studies, but many of these have centered on large animal facilities with various *Salmonella enterica* serotypes as the causative organisms.[5-7] Specific reports of nosocomial infection in dogs and cats remain limited.[5] Since 1978, organisms such as *Serratia marcescens, Salmonella* spp, *Clostridium perfringens, Acinetobacter baumannii, Escherichia coli,* and *Clostridium difficile* have been implicated as causes of nosocomial infection in dogs and cats.[5,8-12] The bacteria responsible for nosocomial infection in ICUs originate either from the patient's own endogenous flora or from exogenous sources. Nosocomial infections derived from endogenous flora may occur in patients receiving chemotherapy, glucocorticoid therapy, or antibiotic therapy. In contrast to endogenous infections, exogenous infections are more likely to be preventable by standard or specific precautions devised to reduce the overall rate of transmission.[13] A review of nosocomial infections in veterinary medicine provides data on the prevalence of urinary tract infections, surgical site infections, bloodstream infections, pneumonia, and diarrhea.[14]

12.4 RISK FACTORS

Although ill defined in veterinary medicine, independent risk factors for nosocomial infection acquisition in the critically ill patient can be extrapolated from human studies. Prolonged length of hospital stay, mechanical ventilation, and indwelling devices, such as intravascular or urinary catheters and nasogastric or endotracheal tubes, are well-recognized risk factors.[1] Many intrinsic, patient-related factors have also been identified and include patient demographics (e.g., age, gender), comorbidities, and severity of underlying illness, which is the most widely reported risk factor. Patient-specific risk factors are related to general health and immune status, respiratory status, neurologic status, and fluid status. A significant risk factor in the ICU is trauma, especially when associated with open fractures. Several less well-acknowledged factors have also been suggested as contributing factors. Among them, understaffing and overcrowding in the ICU have been well documented as causes of cross-transmission of nosocomial infections.[1]

12.5 MULTIPLE ANTIBIOTIC-RESISTANT NOSOCOMIAL PATHOGENS

In an excellent review of the problem of antimicrobial drug use and resistance in veterinary medicine, Prescott and colleagues state that, “Despite a possible wealth of data in filing cabinets in veterinary clinical microbiology laboratories around the world, there have been virtually no systematic investigations of changes in antimicrobial drug resistance in bacteria isolated from companion animals over time, using standard methodologies for assessing resistance.”[15] The situation has changed little since that statement was made in 2002.

Although it is often speculated that organisms isolated from nosocomial infection outbreaks in veterinary patients now have an increasingly broad spectrum of antimicrobial resistance, there are no active nosocomial infection surveillance systems in this field. Much of the antibiotic resistance data are derived from “local” surveillance, and a lack of standardization results in data that are incomparable from one setting to another.[16] In terms of the impact of multidrug-resistant (MDR) bacteria with regard to nosocomial infection, the data that have been published agree that resistant bacteria can reduce the effectiveness of management.[15]

Data on trends in resistance patterns among nosocomial pathogens from veterinary sources are few, but the wealth of surveillance data from human health care systems can often be used as a predictor of what to expect from nosocomial pathogens in veterinary patients.[17-19] Local surveillance of antibiotic resistance in animal isolates is preferred, but in the absence of such data, extrapolation from human surveillance data is encouraged.

Bacterial resistance to β-lactam antibiotics and the β-lactamase inhibitors is becoming increasingly common and threatens to reduce the clinical spectrum of these drugs. In particular, organisms that produce extended-spectrum β-lactamases (ESBLs) and plasmid-mediated AmpC enzymes are posing unique challenges in clinical situations.

Although the prevalence of ESBLs is not known, it is thought to be increasing, and in many parts of the world 10% to 40% of strains of *E. coli* and *K. pneumoniae* produce such enzymes. Novel β-lactamases are also becoming especially important among diverse gram-negative pathogens such as *Pseudomonas aeruginosa, S. enterica* serotype typhimurium, *Proteus mirabilis,* and *A. baumannii.* [20] The source of these novel enzymes is unknown, but their presence on plasmids and ready transferability among pathogens of different genera are of concern. Organisms that produce ESBLs are found commonly in those areas of the hospital environment where antibiotic use is frequent and the patient's condition is critical, and these resistant organisms cause increased morbidity and mortality.[20]

12.6 ZOONOSES

The simplest definition of a *zoonosis* is a disease that can be transmitted from animals to humans. A more technical definition is a disease that normally exists in animals but that can infect humans. Some authors further subdivide the concept into zooanthroponosis, infections that humans can acquire from animals, and anthropozoonosis, a disease of humans that is transmissible to other animals. A comprehensive literature review has identified 1415 species of infectious organism known to be pathogenic to humans and out of these, 868 (61%) are zoonotic.[21] Overall, 19% are viruses or prions, 31% are bacteria or rickettsia, 13% are fungi, 5% are protozoa, and 32% are helminths. Thirty-five percent of zoonoses can be transmitted by direct contact, 61% by indirect contact and 22% by vectors, and for 6%, 50 the transmission route is unknown. Only 33% of zoonotic species are known to be transmissible between humans 51 and only 3% are considered to have their main reservoir in human populations; the main reservoir of the remainder is in animal populations. Zoonoses are more likely to be transmitted by indirect contact or vectors, and are less likely to be transmitted by direct contact when compared with all pathogens.

The list of zoonoses found in animals in the ICU is long, but because some organisms are generally more prevalent, they will have a greater potential for transfer to humans and to cause disease. The enteric pathogens, such as *Campylobacter, Salmonella, C. difficile,* and *E. coli* are commonly isolated from animals in the ICU, and all of these organisms have been responsible for nosocomial outbreaks in that setting.[6,7,12] *Campylobacter* species can occur in large numbers as commensals in companion animals, and there is a strong correlation between diarrhea and the ability to recover *C. jejuni* from healthy dogs. *Salmonella* on the other hand, is not a normal commensal of dogs and cats and its presence in feces likely indicates infection. Enteropathogenic *E. coli* (EPEC) have been isolated from dogs and cats with enteritis, and strains have emerged as important causes of diarrhea in puppies. *E. coli* is also the most common cause of urinary tract infections in dogs and cats in the ICU, and many strains are now resistant to a wide spectrum of antimicrobial agents. Zoonotic transmission of resistant urinary isolates of *E. coli* from companion animals to humans has been suggested.[22] *C. difficile* and *Enterococcus* species are now considered emerging zoonotic agents, and this is also true of *S. aureus,* particularly methicillin-resistant *S. aureus* (MRSA).

Pathogenic *Leptospira* spp have the potential to infect humans and also cause nosocomial infection in animals housed with infected or shedding animals (see Chapter 135, Acute Renal Failure). Leptospires often colonize proximal convoluted kidney tubules and may be excreted in urine for extended periods by dogs that show no clinical signs. The carrier state may be as short as a few days or may extend throughout the life of the animal. The primary routes of infection for dogs are direct contact (oral, conjunctival), venereal and placental transfer, bite wounds, and ingestion of contaminated meat.

The cutaneous mycoses of animals caused primarily by *Microsporum* and *Trichophyton* species are well recognized zoonotic agents that cause ringworm in humans and can be acquired from contact with infected animals or from fomites. Dermatophyte spores gain entry to the skin through minor trauma such as abrasions.

Uncommon, perhaps emerging, zoonotic agents that may be found in veterinary patients may also include a variety of *Mycobacterium* species, *Malassezia pachydermatis, Candida albicans, Brucella canis,* and MDR strains of both *P. aeruginosa* and *K. pneumoniae*. Undoubtedly, as veterinary nosocomial infection surveillance systems improve, a host of additional pathogenic or MDR organisms will be reclassified as zoonotic.

12.7 EMERGING NOSOCOMIAL INFECTIONS IN DOGS AND CATS

Consistent with a generalized increase in β-lactam resistance, several reports in the veterinary literature have described an increase in the prevalence of MRSA strains isolated from dogs and cats.[23,24] In 1998, a Korean veterinary hospital representative reported three small nosocomial clusters of MRSA infection in hospitalized dogs. Isolates were obtained from 12 dogs and were recovered from the anterior nares, catheters, conjunctiva, a postoperative wound, and a skin lesion.[25] A further description of MRSA infection in dogs from the United Kingdom reported that in 8 of 11 dogs the infection was likely contracted during surgical procedures, the most common of which were repair of traumatic fractures.[26] Of the 11 dogs, 3 suffered from chronic pyoderma that was not responsive to routine antibiotic treatment. The MRSA infection resolved or improved in 9 of those cases after appropriate antibiotic therapy. Treatment of individual MRSA cases must begin with review of the antibiotic susceptibility profile of individual isolates, and selective antimicrobial therapy should be based upon those results.

In addition to MRSA, methicillin-resistant *S. intermedius* and *S. schleiferi* may present a more pressing threat to veterinary medicine. In a survey done at the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania, the rates of methicillin resistance in these three pathogens isolated between 2003 and 2004 were 32%, 17%, and 49%, respectively (unpublished data).

C. difficile was implicated as the causative organism in an outbreak of diarrhea in dogs in a small animal veterinary teaching hospital.[12] Of note, no cases were identified in the ICU, and this was attributed to stringent infection control measures. *C. difficile*–associated disease (CDAD) occurs as a result of intestinal colonization and toxin production by toxigenic strains. A diagnosis of CDAD is made following detection of both an enterotoxin, designated Toxin A, and a cytotoxin, designated Toxin B, in fecal specimens. Some animals are known to carry toxigenic strains of *C. difficile* without toxin production, so demonstration of the organism in feces by anaerobic culture is not confirmatory. Sources of nosocomial *C. difficile* include colonized or infected animals, indirect contact via hospital personnel, or environmental reservoirs of potentially pathogenic spores that are known to be resistant to commonly used disinfectants. Treatment of CDAD depends on a number of factors that include co-infection with additional enteric pathogens. Metronidazole or vancomycin is generally the antibiotic of choice.

Vancomycin-resistant *Enterococcus faecium* (VRE) has not yet been implicated in nosocomial infections of dogs and cats. However, VRE has been identified in a canine urinary tract infection, and monitoring at veterinary teaching hospitals in the United States and Europe has revealed VRE carriage in healthy dogs.[27,28] Most VRE isolates are highly resistant to many other antimicrobial classes, and the gene responsible for vancomycin resistance is resident on a transposable element; the exchange of this element has been demonstrated between human and canine *E. faecium*. Therefore the use of vancomycin alone may not be a necessary prerequisite for selection of VRE in small animals.[27]

Overall, the number of reports of infection or colonization in animal species of pathogens that have traditionally been thought to have a reservoir only in humans has increased since the earliest reports of MRSA in the 1960s and 1970s. This trend can be considered a significant public health concern given the potential for direct spread of MDR pathogens between humans and animals. It is reasonable to assume that infected dogs and cats can serve as 51 reservoirs for these pathogenic organisms. However, the alternative hypothesis, that humans can also be a reservoir for MDR infectious agents that can be transmitted to dogs and cats, now seems equally feasible.

12.8 NOSOCOMIAL INFECTION PREVENTION AND CONTROL

The reservoirs of nosocomial pathogens include humans, animals, fomites, air currents, water and food sources, insects, and rodents, and it has long been known that the spread of pathogens in hospitals occurs primarily via the hands of personnel.[1] Therefore frequent hand washing is of the utmost importance and the use of gloves in handling patients may also help to decrease the incidence of nosocomial infection. In 1989, Murtaugh and Mason proposed that nosocomial infection control committees be established in veterinary hospitals, especially at the larger teaching and referral centers.[29] Some veterinary institutions were receptive to this proposal, but there are still no national or international standards for veterinary hospital infection control. Much of what is written is borrowed from human health care guidelines, and worldwide surveillance statistics of veterinary nosocomial infection rates are not available.

The guidelines for prevention and control of nosocomial infection are simple and comprise three main approaches. First, methods are needed to prevent cross-contamination and to control potential sources of pathogenic microorganisms that can be transmitted from patient to patient or from hospital personnel to patient. Secondly, guidelines are needed to direct the appropriate use of prophylactic, empiric, and therapeutic antimicrobial use. Finally, strategies to limit the emergence or spread of MDR pathogens should be developed and targeted against organisms known to be prevalent in individual institutions. Some of these approaches may at first seem to be restrictive, but infection control guidelines are intended only to improve the process of care. Infection control measures when instituted in human health care settings have been unpopular, and compliance is difficult to maintain. It has been suggested that noncompliance is connected with many aspects of human behavior, including the yearning of human beings for liberty, the false perception of an invisible risk, and the underestimation of individual responsibility in the epidemiology of the institution.[1]

In conclusion, the importance of nosocomial transmission, particularly in the ICU, cannot be overemphasized. Although the intrinsic risk factors of individual animal patients for the development of nosocomial infection are difficult to assess, the risk of transmission of pathogenic and MDR organisms can and should be reduced to a minimum whenever possible.

12.9 SUGGESTED FURTHER READING*

P Eggimann, D Pittet: Infection control in the ICU. *Chest*. **120**, 2001, 2059, *This is an excellent overview targeted at ICU physicians in human health care that discusses the principles of infection control and their importance*.

PS Morley: Biosecurity of veterinary practices. *Vet Clin North Am Food Anim Pract*. **18**, 2002, 133, *This paper discusses the need for biosecurity programs in veterinary practices and describes a practical approach for developing biosecurity practices that are tailored to individual facilities*.

RJ Murtaugh, GD Mason: Antibiotic pressure and nosocomial disease. *Vet Clin North Am Small Anim Pract*. **19**, 1989, 1259, *This paper discusses nosocomial infection in veterinary hospitals, in association with antibiotic usage. Strategies for control are outlined*.

JS Weese: Barrier precautions, isolation protocols, and personal hygiene in veterinary hospitals. *Vet Clin North Am Equine Pract*. **20**, 2004, 543, *This paper describes hospital veterinary infection control policies*.

* See the CD-ROM for a complete list of references

13 Chapter 13 Enteral Nutrition

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13.1 KEY POINTS

- The goal of enteral nutrition is to provide the patient with adequate caloric and nutrient intake to prevent the adverse consequences of malnutrition.
- Every critically ill patient must have an assessment performed to determine an appropriate nutrition plan. Patient reevaluation and nutrition plan reassessment need to occur throughout the hospitalization.
- As a general guideline, enteral feeding as far proximal as possible in the gastrointestinal (GI) tract is the preferred route of delivering nutritional support.
- Feasibility of enteral nutrition is based on patient factors such as GI function and ability to protect the airway, as well as nonpatient factors such as cost, predicted length of hospitalization, technical expertise, and level of patient monitoring.
- The daily caloric goal for most critically ill patients will be the resting energy requirement. Evaluating whether a patient achieves this level of intake requires detailed feeding orders and documentation of patient intake.
- Potential complications of enteral nutrition include patient factors such as inadequate intake, GI side effects, metabolic derangements, and infectious complications, as well as nonpatient factors such as mechanical complications related to the feeding device.

13.2 INTRODUCTION

The goal of enteral nutrition is to provide the patient with adequate caloric and nutrient intake via the gastrointestinal (GI) tract in order to prevent the adverse consequences of malnutrition. Hospitalized patients frequently have decreased voluntary food intake for many reasons, including nausea, pain, and anxiety. At the same time, critically ill patients have metabolic alterations mediated by catecholamines, corticosteroids, and inflammatory mediators such as interleukin-1 and tumor necrosis factor (TNF)-α, which alter metabolism resulting in a catabolic state.[1] Decreased voluntary intake coupled with a catabolic state places critically ill patients at high risk for malnutrition, necessitating nutritional support. Malnutrition in the critically ill patient leads to depletion of endogenous proteins, which may have serious adverse effects on tissue synthesis, immunocompetence, maintenance of gut integrity, and intermediary drug metabolism.[2] Malnutrition in humans is associated with increased complication rates, duration of hospitalization, and cost.[3] While analogous studies have not been conducted in veterinary medicine to date, it seems reasonable to assume that comparable outcomes would be expected in malnourished veterinary patients.

13.3 NUTRITIONAL ASSESSMENT

Intervention begins with a nutritional assessment of the individual patient. The goal is to determine whether the patient is at low, moderate, or high risk for malnutrition. The process begins with a review of the history and medical record. The clinician obtains a comprehensive, detailed dietary history regarding all foods ingested before and during the current illness, including pet foods, table foods, and nutritional supplements. Both a subjective assessment of appetite and an objective determination of the amount of food consumed are recorded. The logistics of feeding management, such as number of meals per day, are noted. The clinician must assess nutritional adequacy because clients frequently feed their pets unbalanced diets during periods of illness to encourage intake. Past or current GI signs should be noted because these may affect the nutritional plan. A thorough medication history is required because some medications affect appetite or nutrient metabolism.

Veterinary patients who have not consumed or are not anticipated to consume their resting energy requirement (RER) for 3 to 5 days or who have lost 10% of usual or optimal body weight (5% for pediatric patients) are at high risk of malnutrition and require nutritional support once their immediate hydration, hemodynamic, acid-base, blood glucose, and electrolyte abnormalities are stabilized.[2]

A physical examination is performed to assess body weight, body condition, and muscle mass. The clinician should be aware that a patient might have excessive fat stores but low muscle (lean body) mass.[4] The metabolic derangements of critical illness often lead to a precipitous loss of lean body mass, placing the patient at high risk for protein calorie malnutrition. Careful physical examination may also detect signs of malnutrition such as poor skin or coat quality. Physical examination may reveal abnormalities that preclude certain feeding modalities. For example, facial trauma necessitates enteral feeding that bypasses the oral cavity.

Routinely measured laboratory parameters such as complete blood count, serum biochemistry, and urinalysis are poor indicators of overall nutritional status. However, hypoalbuminemia, anemia, or low blood urea nitrogen (BUN) levels may occur secondary to malnutrition. The underlying disease factors into risk assessment for malnutrition and often dictates several components of the nutrition plan, including route of delivery and the nutrient composition of the diet. Some diseases such as protein-losing enteropathy, protein-losing nephropathy, chylothorax, burns, and draining wounds cause excessive loss of body protein, requiring an aggressive nutrition plan to meet caloric and protein needs. Conversely, a patient with protein intolerance such as hepatic encephalopathy might need a plan to meet the patient's caloric needs without further elevating nitrogenous wastes in the bloodstream.

History, physical examination, and diagnostic findings determine the patient's risk for malnutrition. As a general 53 54 guideline, higher risk patients require a more aggressive nutritional intervention plan and closer monitoring for both positive response and complications of dietary intervention. However, the risk of malnutrition may change over time. Patient reevaluation and nutrition plan reassessment must occur throughout hospitalization.

13.4 DETERMINING THE ROUTE OF NUTRITIONAL SUPPORT

13.4.1 Enteral Versus Parenteral

Nutritional support can be delivered via the GI tract (enteral route), via the vasculature (parenteral route), or using a combination of the two. Both routes require a hemodynamically stable patient with no major acid-base or electrolyte abnormalities. The route of nutrient delivery is determined by patient factors such as GI function and ability to protect the airway, and nonpatient factors such as cost, predicted length of hospitalization, technical expertise, and level of patient monitoring. Enteral feeding is preferable to parenteral feeding because it is physiologically sound, less costly, and safer.[5] The physiologic benefits of enteral feeding include prevention of intestinal villous atrophy, maintenance of intestinal mucosal integrity, which decreases the risk of bacterial translocation, and preservation of GI immunologic function. Contraindications for enteral feeding are uncontrolled vomiting, GI obstruction, ileus, malabsorption or maldigestion, or inability to protect the airway. However, if the patient is unable to protect the airway, the clinician may select a route of nutrient delivery distal to the pharynx or esophagus if the concern is aspiration during swallowing, or distal to the pylorus if the concern is aspiration during vomiting or regurgitation. Figure 13-1 outlines the decision process for selecting an appropriate enteral feeding route.

13.4.2 Oral Intake Versus Enteral Feeding Device

When enteral feeding is appropriate, the clinician selects the mode of nutrient delivery, sets a caloric goal, and chooses an appropriate diet. Enteral feeding as far proximal in the GI tract as the patient can tolerate is preferred. Voluntary oral intake has distinct advantages. It requires no special equipment or techniques and allows the owner to participate in patient care. If the oral route is selected, the clinician must write specific feeding orders. The technical staff offers the amount written on the feeding orders and records the amount consumed. The clinician then determines if the nutrition goal was met. If intake does not meet the goal, the clinician reassesses the patient, diet, and environment. The clinician may change the diet (e.g., more palatable diet, warming the food) or change the environment (e.g., quieter ward, owner feeding the pet). Syringe feeding a liquid or blenderized pet food may be attempted for 1 to 2 days but frequently becomes too stressful and time consuming. If the patient shows any signs of nausea, oral feeding should be discontinued immediately, because this can lead to a learned food aversion. Medication to ameliorate nausea and an alternative feeding method should be considered.

An enteral feeding tube removes the variable of voluntary intake. The technical staff delivers a prescribed amount of a specific diet via the feeding tube according to orders written by the veterinarian. These tubes are well tolerated by veterinary patients. A retrospective owner survey concluded that owners were comfortable managing their cats at home with esophagostomy and percutaneous endoscopic gastrostomy tubes.[6] However, enteral feeding device placement usually requires sedation or anesthesia and technical skill. Technicians and owners must be taught how to use feeding devices and monitor for complications. Table 13-1 outlines advantages and disadvantages of the various forms of enteral access used in veterinary patients.

13.5 ENTERAL FEEDING TUBES

13.5.1 Nasoesophageal or Nasogastric Tubes

A 3.5 to 8 Fr silicone or polyurethane feeding tube may be placed through the nares into the distal esophagus (nasoesophageal [NE]) or into the stomach (nasogastric [NG]) (Color Plate 13-1). NE tubes are preferred because the risk of gastric reflux increases if the tube passes the lower esophageal sphincter. However, NG tubes allow for gastric decompression and measurement of gastric residual volume. Radiographic confirmation of correct placement is recommended.

An advantage of NE and NG tubes is that they can be placed easily under local anesthetic or light sedation.[7] This is a good option for patients that are poor candidates for general anesthesia. Facial trauma may preclude placement of this type of tube, and it should not be used in a patient with respiratory disease because it may exacerbate respiratory compromise. Any patient that receives enteral nutrition must have a functional GI tract and the ability to guard the airway if vomiting or regurgitation occurs.

Because only small-bore tubes are used, diet selection is limited to liquids. NE and NG tubes are best for short-term (7 to 14 days) feeding because they can be irritating. An Elizabethan collar (E-collar) and close monitoring are required because the pet may attempt to dislodge the tube. In addition, sneezing or vomiting may dislodge the tube, requiring reassessment for correct placement. Complications associated with NE or NG tubes include epistaxis, rhinitis, sinusitis, dacryocystitis, inadvertent placement or dislodgement of the tube into the airway, esophageal irritation, reflux, or clogging of the tube.

13.5.2 Esophagostomy Tube

A larger feeding tube (usually a 12 to 14 Fr tube for cats and up to a 22 Fr for larger dogs) can be placed in the proximal esophagus at the midcervical level, with the tip positioned in the distal esophagus (Color Plate 13-2). The esophagostomy tube (E-tube) has several advantages. Veterinary patients appear to tolerate them quite well. They can be used for fairly long periods (weeks to months) in both the hospital and outpatient settings. The larger tube allows for a wider selection of diets, including blenderized canned pet foods. The tube can be used in patients with facial or oral disease that precludes NE tube placement. As with the NE tube, the patient must have normal GI function, including normal esophageal function and the ability to protect the airway.

Placement of this tube requires general anesthesia and technical skill, although the technique is relatively simple and well described.[8-12] E-tubes can be used for feeding as soon as the patient recovers from anesthesia and can be removed by the clinician at any time. Risks associated with E-tubes include placement in the airway or mediastinum and damage to cervical vascular or nerve tissue. As with the NE tube, a lateral radiograph should be used to verify placement. Complications include cellulitis or infection at the tube site, patient dislodgement, esophageal irritation and reflux, displacement during vomiting or regurgitation, and clogging of the tube.

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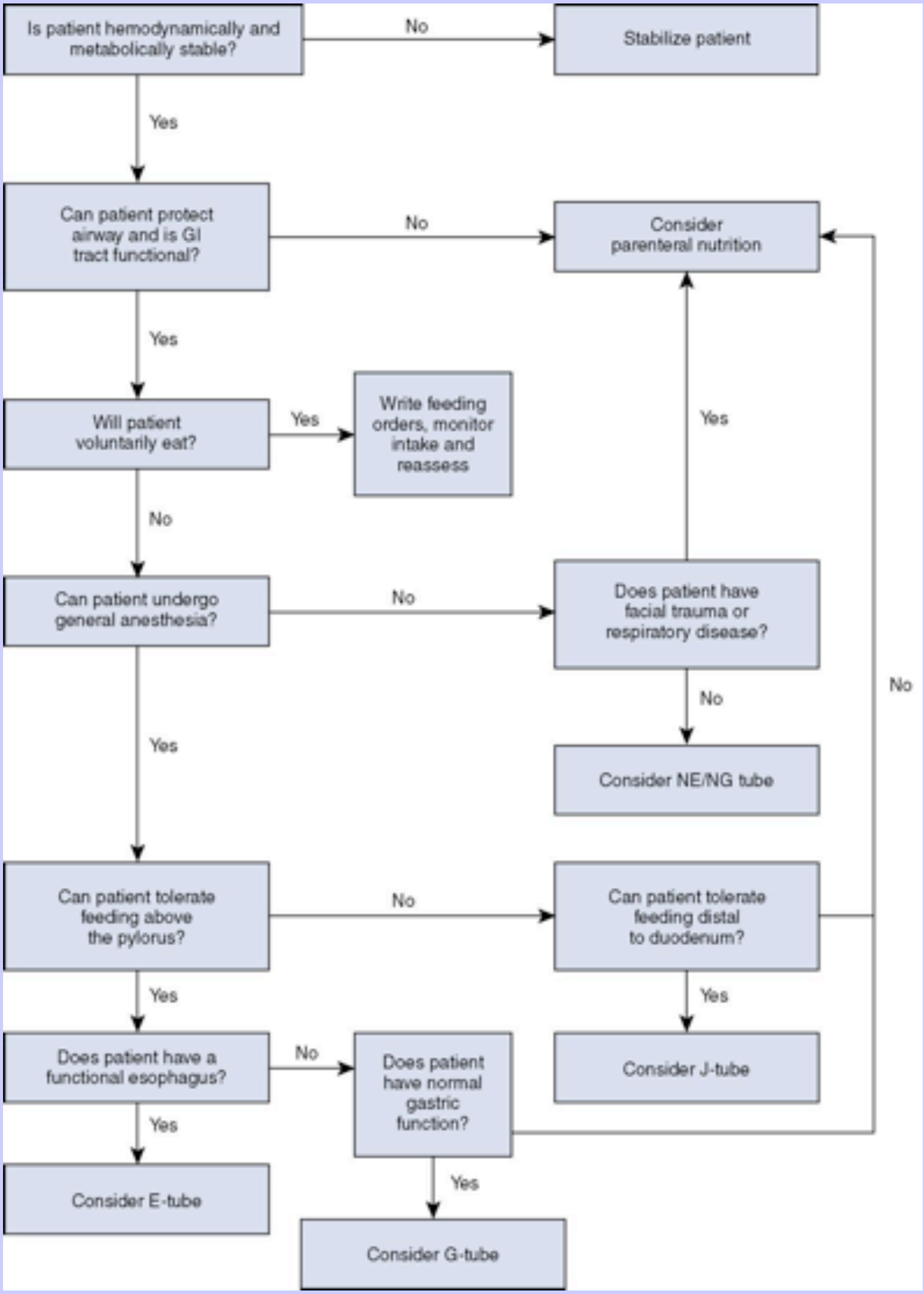
Figure 13-1 Decision tree for selecting enteral feeding route. GI, Gastrointestinal.


Is patient hemodynamically and metabolically stable?
No
Stabilize patient
Yes
Can patient protect airway and is GI tract functional?
No
Consider parenteral nutrition
Yes
Will patient voluntarily eat?
Yes
Write feeding orders, monitor intake and reassess
Yes
No
Can patient undergo general anesthesia?
No
Does patient have facial trauma or respiratory disease?
No
No
Yes
Consider NE/NG tube
Can patient tolerate feeding above the pylorus?
No
Can patient tolerate feeding distal to duodenum?
Yes
Yes
Does patient have a functional esophagus?
No
Does patient have normal gastric function?
Consider J-tube
Yes
Consider E-tube
Yes
Consider G-tube

13.5.3 Gastrostomy Tube

Larger (usually 16 to 22 Fr mushroom-tipped) feeding tubes can be placed directly in the stomach via surgical placement,[2,13] endoscopic guidance,[2,14] or blind technique using a gastrostomy tube placement device.[2,12-15] All techniques require longer time under anesthesia and more technical skill than is needed for E-tube placement. The 55
56 percutaneous endoscopic gastrostomy and blind technique avoid doing a laparotomy, but if the patient is undergoing abdominal surgery, surgical placement is preferable because the surgeon can visualize placement and pexy the stomach to the abdominal wall. Endoscopic placement is preferred over a blind technique because it allows visualization of the gastric placement site and decreases the risk of iatrogenic injury to abdominal viscera during placement.[12]

Table 13-1 Advantages and Disadvantages of Enteral Feeding Devices

Enteral Feeding Device	Advantages	Disadvantages
NE or NG tube	Ease of placement No general anesthesia NG tube allows for gastric decompression	Limited to liquid diets Short term (<14 days) Can be irritating; requires E-collar Can dislodge if patient sneezes or vomits Contradicted in facial trauma or respiratory disease Increased risk of vomiting with NG vs NE tube
Esophagostomy tube	Blenderized pet foods or liquid diets can be used Well tolerated by patient Ease of placement Can feed as soon as patient awakens from anesthesia Can be removed at any time Good long-term option	Requires general anesthesia Risk of cellulitis or infection at site Can dislodge if patient vomits Can cause esophageal irritation or reflux if malpositioned
Gastrostomy tubes	Blenderized pet foods or liquid diets can be used Well tolerated by patient Good long-term option	Requires general anesthesia Risk of cellulitis or infection at site Risk of peritonitis Must wait 24 hours after placement before feeding Must wait 10 to 14 days before removing
Jejunostomy tube	Requires liquid diet Able to feed distal to pylorus and pancreatic duct	Requires general anesthesia Technically more difficult to place Risk of cellulitis or infection at site Risk of peritonitis Risk of tube migration with secondary GI obstruction Must wait 24hours after placement before feeding Requires CRI feeding Requires very close monitoring Short-term option

CRI, Constant rate infusion; *GI,* gastrointestinal; *NE,* nasoesophageal; *NG,* nasogastric.

The gastrostomy tube (G-tube) provides nutrients distal to the esophagus, providing enteral feeding to patients with esophageal disease. The G-tube is well tolerated, permits bolus meal feedings, and is appropriate for long-term at-home feeding.[6,16] As with the E-tube, the option of blenderized pet foods allows a wider diet selection. The patient must tolerate feeding above the pylorus without vomiting. The tube cannot be used for the first 24 hours after placement to allow return of gastric motility and formation of a fibrin seal at the stoma. The tube should not be removed until the stomach has adhered to the body wall to prevent stomach content leakage and secondary peritonitis. The tube is typically left in place for at least 10 to 14 days, or longer in more severely compromised or malnourished patients. Major complications associated with G-tubes include abdominal visceral injury during percutaneous placement or peritonitis if stomach contents leak into the abdominal cavity secondary to tube displacement or dehiscence. As with any surgically placed feeding device, cellulitis or infection at the stoma site is possible. Improperly placed G-tubes may cause a pyloric outflow obstruction. A G-tube requires closer monitoring and is more costly than techniques previously described.

13.5.4 Jejunostomy Tube

A small-bore feeding tube (usually 5 to 8 Fr) can be placed directly in the proximal jejunum. Feeding distal to the pylorus provides enteral nutrition to patients unable to tolerate gastric feedings. Indications for jejunostomy tubes (J-tubes) include gastroparesis, uncontrolled vomiting, canine pancreatitis, and inability to protect the airway. The most common method used for placing J-tubes is surgically during laparotomy,[17,18] although transpyloric placement techniques via nasojejunal or gastrojejunal feeding tubes have been described.[19-21] Surgical placement allows visualization of tube position and a pexy of the bowel to the abdominal wall. Transpyloric techniques are less invasive, with nasojejunal tubes eliminating the risk of bowel content leakage into the peritoneum. However, transpyloric placement requires advanced technical skill and either endoscopic or fluoroscopic guidance. J-tubes can be used for a moderately short period (days to weeks). Surgically placed or gastrojejunal tubes cannot be used until a fibrin seal has formed at the body wall.

The small diameter of J-tubes limits diet selection to liquids. To minimize the risk of abdominal cramping and vomiting, constant infusion is preferred over bolus feeding. This requires more diligent patient monitoring and does not allow for at-home feeding under most circumstances.

Complications associated with J-tubes include peristomal cellulitis or infection, peritonitis secondary to leakage, retrograde migration of the J-tube, intestinal obstruction secondary to tube migration, and clogging of the tube.

13.6 DETERMINING THE AMOUNT TO BE FED

Hospitalized patients should initially be fed to meet the RER, defined as the amount of energy (calories) needed to maintain homeostasis in the fed state in a thermoneutral environment.[2] Calorimetry is not used in the clinical veterinary setting, so estimates of RER can be calculated by allometric formulas such as $70BW_{kg}^{0.75}$. Calculations for obese patients should be based on optimal body weight to prevent overfeeding. “Illness factors” are no longer widely used in critical care nutrition.[22] The patient must be reassessed to see if the initial caloric estimate is appropriate. The goal during hospitalization is to maintain body weight (excluding fluctuations due to hydration status) and lean body mass. Overfeeding is associated with GI and metabolic complications. Certain disease conditions such as sepsis, head trauma, or burns may require increased caloric intake if the above goals are not met by RER. In patients with prolonged anorexia, gastrointestinal compromise, or metabolic derangements, the caloric goal should be achieved over several days. Typical feeding protocols might provide 30% to 50% RER on day 1, with the goal of reaching full RER over the next several days.

13.7 SELECTING THE DIET

13.7.1 Patient Variables

Highly digestible nutrients from high quality sources should be selected for critical care patients. A patient with a poor appetite may benefit from a more calorie-dense diet because a smaller volume of food will meet the caloric goal. The clinician must determine if any macronutrients or micronutrients should be altered due to the patient's disease condition. For example, enteral protein intake should be 4 to 6 g of protein per 100 kcal (15% to 25% of total energy) for dogs and 6 or more g of protein per 100 kcal (25% to 35% of total energy) for cats.[22] Certain disease conditions such as hepatic encephalopathy may require the clinician to select diets closer to the minimum protein requirement to help prevent protein intolerance. However, when a lower protein diet is fed, adequate calorie and protein intake is essential in order to minimize the risk of protein malnutrition. Conversely, disease conditions associated with a high degree of protein loss may require a diet replete in protein. Other examples of nutrient modulation include sodium in patients with congestive heart failure and fat in patients with hyperlipidemia, canine pancreatitis, and GI diseases leading to fat malassimilation.

13.7.2 Nonpatient Variables

Nonpatient variables contribute to diet selection. Small-diameter NE-, NG-, or J-tubes require liquid diets. Financial constraints and cost of diets may factor into the selection process. Choices are limited by availability (i.e., the hospital inventory) and the clinician's knowledge of various products.

13.8 MONITORING THERAPY

Nutritional assessment occurs at least daily. The clinician reviews past feeding orders to determine if the appropriate diet plan was instituted and if the patient achieved the set goals. If the patient did not meet the dietary goal, the clinician must determine whether the cause was related to patient issues (e.g., nausea, unpalatable diet) or nonpatient issues (e.g., improperly written orders, orders not followed, feeding with-held for procedures). The clinician then updates the plan. Monitoring of body weight daily, hydration status, and laboratory values such as blood glucose, total solids, lipemia check, blood urea nitrogen, and electrolytes must be done to assess the response to dietary intervention and to check for complications. The frequency and specifics of monitoring depend on the patient's disease condition, the mode of dietary intervention, and financial constraints. Patients that are critically ill and those receiving aggressive dietary intervention require the closest monitoring.

13.9 PREVENTING AND MANAGING COMPLICATIONS

13.9.1 Patient-Related Complications

Many feeding complications can be prevented by proper patient evaluation, selection of the appropriate route and amount of nutrient delivery, understanding of the risks associated with the specific feeding plan, and close patient monitoring. Most enteral feeding complications are minor but aspiration, premature dislodgement of a gastrostomy or enterostomy tube, and certain metabolic abnormalities can be life threatening.[23] GI intolerance may manifest as vomiting, diarrhea, or ileus. This complication can compromise the ability to continue enteral feeding. The clinician should assess the feeding plan to confirm that daily intake does not exceed the patient's energy requirements (approximately RER in most cases) and that the day's feeding is divided into multiple small meals. Food should be warmed to body temperature for tube feeding. The patient's disease condition or medications may contribute to nausea, vomiting, ileus, or diarrhea. Altering medications or providing antiemetics or prokinetic agents may allow for continued enteral feeding.

Metabolic complications can arise if a patient is unable to assimilate certain nutrients. For example, a patient with glucose intolerance may need a dietary formulation low in simple carbohydrates to modulate hyperglycemic episodes. Anticipating specific intolerances during nutritional assessment and setting conservative caloric goals not to initially exceed RER will minimize the risk.[23] Refeeding syndrome is a life-threatening metabolic complication that may occur in patients after prolonged anorexia or in certain catabolic states. In this syndrome, on reintroduction of feeding, there is a rapid shift of key intracellular electrolytes from the vascular to the intracellular space causing life-threatening hypokalemia, hypophosphatemia, or hypomagnesemia. This electrolyte abnormality can occur within days of resuming enteral feeding.[24] At-risk patients should be fed conservative amounts initially and monitored closely and electrolyte abnormalities corrected via parenteral or enteral replacement.

Aspiration is a potentially life-threatening complication that can be minimized by careful patient selection and close monitoring. Infections may occur at the peristomal site, along fascial planes, or within the peritoneum. Infectious complications can be minimized with proper tube placement, careful monitoring of tube sites, and basic hygiene during the preparation and delivery of food. 57

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13.9.2 Nonpatient-Related Complications

Mechanical complications include obstructed tubes or tube migration. Clogging can be prevented by proper management such as flushing with warm water before and after every use. One should avoid using the feeding tube to administer medications. If the tube becomes obstructed, flushing with warm water under alternating pressure and suction may dislodge the debris. A “recipe” for unclogging feeding tubes with pancreatic enzyme, sodium bicarbonate, and water has been described.[25] Proper technique in placing and suturing tubes will minimize the risk of tube migration and dislodgement. E-collars, bandages, and patient monitoring help prevent the patient from removing a tube. The tube should be marked with indelible ink where it exits the body so that migration can be detected. Radiographs can be taken if tube migration is suspected, with use of a contrast agent if leakage into the peritoneal space is suspected. Dislodged or migrated tubes should never be used for feeding without verifying placement.

13.10 SUGGESTED FURTHER READING*

CA Buffington, C Holloway, SK Abood: In *Manual of veterinary dietetics*. 2004, Elsevier, St Louis, *An excellent, easy-to-understand reference for veterinarians and veterinary technicians interested in learning the basics of small animal clinical nutrition.*

E Han: Esophageal and gastric feeding tubes in ICU patients. *Clin Tech Small Anim Pract*. **1**(1), 2004, 22–31, *Excellent step-by-step instructions for placing NE, esophagostomy, and percutaneous and blind-placement gastrostomy tubes.*

KE Michel: Preventing and managing complications of enteral nutritional support. *Clin Tech Small Anim Pract*. **1**, 2004, 49, *Excellent discussion of enteral feeding complications in the clinical setting.*

J Prittie, L Barton: Route of nutrient delivery. *Clin Tech Small Anim Pract*. **1**, 2004, 6, *Concise review of the routes of enteral nutrition delivery.*

RL Remillard, PJ Armstrong, DJ Davenport: Assisted feeding in hospitalized patients: enteral and parenteral nutrition. In MS Hand, CD Thatcher, RL Remillard, PR Roudebush (Eds.): *Small animal clinical nutrition*. ed 4, Kan, 2000, Mark Morris Institute, Topeka, *A comprehensive textbook covering basic principles of small animal nutrition including sections on pet foods, and the nutritional management of healthy and clinically ill patients*.

* See the CD-ROM for a complete list of references

14 Chapter 14 Parenteral Nutrition

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14.1 KEY POINTS

- Parenteral nutrition (PN) is provided by the intravenous (IV) route and is used when nutritional support is indicated for a patient but enteral delivery is not feasible.
- The three basic requirements that must be met for parenteral nutritional support are: (1) the ability to obtain and maintain appropriate vascular access aseptically, (2) the ability to provide 24-hour nursing care and monitoring, including basic point-of-care serum chemistry evaluation, and (3) the means and the expertise to formulate the PN prescription and compound the nutrient admixture.
- Special considerations for the nutritional assessment of a candidate for PN include assessing vascular access, fluid tolerance, and preexisting conditions that may affect the patient's nutrient tolerance or predispose it to metabolic complications.
- Particular attention should be paid to the catheter site for signs of phlebitis or infection. Daily monitoring of hydration status, fluid tolerance, blood glucose concentration, serum electrolyte values, and evidence of lipemia is indicated.

14.2 INTRODUCTION

PN is provided by the IV route. The intraosseous route can also be used for very small patients such as neonatal dogs and cats. Parenteral delivery is used when nutritional support is indicated for a patient but the enteral route is not feasible. Most commonly this happens because per os feeding is contraindicated, as with a patient experiencing nausea and vomiting or a patient unable to guard its airway and thereby at risk of aspirating stomach contents. PN is also indicated in patients in need of nutritional support who are experiencing gastrointestinal malassimilation and are unable to absorb adequate nutrients by the enteral route.

Although enteral nutrition has many advantages over the parenteral route (see Chapter 13, Enteral Nutrition), in patients for whom enteral nutrition is contraindicated or insufficient, PN can be life sustaining. This technique of assisted feeding has been used successfully in many species, including humans, dogs, cats, horses, cattle, birds, and various exotic species.[1-4]

14.3 TECHNICAL REQUIREMENTS

Parenteral nutritional support may not be feasible in every veterinary practice, but the associated technology and equipment is becoming increasingly accessible and affordable for many small animal hospitals. Three basic requirements must be met in order to provide parenteral nutritional support to a patient. First, it must be possible to obtain and maintain appropriate vascular access aseptically. Second, 24-hour nursing care must be available, along with the ability to do at least basic point-of-care serum chemistry evaluation. And third, there must be the means and the expertise to formulate the PN prescription and compound the nutrient admixture.

14.3.1 Vascular Access

To minimize the risk of line sepsis or drug-nutrient interactions, PN must be delivered through a dedicated venous catheter, although a single dedicated port of a multilumen catheter will suffice. A dedicated line is one that is not used for any other purpose, including blood sampling, hemodynamic monitoring, or delivery of other IV fluids or medications. Because some of the nutrient solutions used to formulate the PN admixture are hyperosmolar, central venous access is preferred. The hyperosmolar PN admixture will be diluted by the rapid blood flow in central vessels, thus greatly reducing the risk of phlebitis. However, both centrally and peripherally inserted central venous catheters can be used. It is possible to dilute solutions sufficiently so that they can be delivered through a peripheral venous catheter, but the resulting increased volume that must be delivered will limit the ability to meet nutritional goals in patients with limited fluid tolerance.

Catheters should be composed of nonthrombogenic materials such as polyurethane or silicone, and peripheral catheters should be as long as practically possible. The line placement should be treated as a surgical procedure, with surgical preparation of the catheter site, draping, and sterile gloves. The catheter site should be covered with a sterile dressing that should be inspected and changed daily.

14.3.2 Monitoring and Nursing Care

The best setting for delivering PN is an intensive care or fluid ward that has 24-hour staffing and the capability of doing basic in-house serum chemistry analysis. Most patients requiring PN are critically ill and will need intensive care and monitoring. Even a relatively stable patient who is receiving PN needs to be in a facility that can provide expert nursing care to properly maintain the central venous catheter and monitor the patient. Although PN can be delivered cyclically, it is best delivered as a constant rate infusion. It will be necessary to monitor various serum chemistry values depending on the patient's underlying condition (e.g., electrolytes, glucose, blood urea nitrogen [BUN], albumin), sometimes multiple times in the course of a day. This will be greatly facilitated by having in-house equipment.

14.3.3 Formulating and Compounding Nutrient Admixtures

Veterinary patients usually are not supported with PN for longer than 1, or at most 2, weeks. Therefore it is rare that a patient would receive a nutrient admixture that was formulated to provide complete nutrition. Generally PN solutions provide energy, protein, and water-soluble vitamins, with the optional addition of electrolytes and some of the trace elements. In addition to knowing how to formulate the PN prescription, it is necessary to have ready access to the special nutrient solutions and to know how to compound these solutions for nutrient admixture (Color Plate 14-1). Nutrient solutions must be combined in the proper order to prevent components from precipitating out of solution or suspension, and the entire process must be done under sterile conditions to prevent microbial contamination. Therefore, unless PN is used frequently in a practice, it is far more practical to find a human hospital or home transfusion service that will compound the solutions on request.

14.4 NUTRITIONAL ASSESSMENT

The task of evaluating a patient for nutritional support has been covered in detail in Chapter 13, Enteral Nutrition. Additional considerations for candidates for PN include assessing vascular access, fluid tolerance, and preexisting conditions that may affect the patient's nutrient tolerance or predispose it to metabolic complications.

Ideally PN should be delivered via a dedicated central line; however, central venous access may be unobtainable or contraindicated. For example, central catheter placement via a jugular vein is contraindicated in patients with head trauma or other conditions predisposing to increased intracranial pressure, those at risk of thromboembolic disease (e.g., protein-losing nephropathy or enteropathy, disseminated intravascular coagulation [DIC], hyperadrenocorticism, or those receiving high-dose glucocorticoids), or patients with severe coagulopathies. Fortunately, central vascular access can still be obtained in most patients by using a peripherally inserted central venous catheter (PICC).

Patients should be evaluated for their ability to tolerate the additional fluids that they will receive from the PN admixture. This will not be a problem for most patients; however, animals experiencing heart failure or oliguria will be at risk of volume overload. For patients with reduced fluid tolerance it is especially important to have central venous access to allow the most concentrated nutrient solutions to be used for formulation of the PN admixture. It may be possible to reduce the volume of the other IV fluids that the patient is receiving to accommodate that of the PN. Even so, there will occasionally be patients for whom it will not be possible to meet nutritional goals with parenteral nutritional support due to fluid intolerance.

Metabolic complications of PN are common,[1,2] but most can be minimized, if not avoided, by evaluating each patient for predisposing conditions such as an impaired ability to metabolize a specific nutrient or eliminate its metabolites. Table 14-1 lists some of the more common metabolic complications seen with PN and the conditions that may predispose to them. By anticipating complications, the PN admixture can be formulated in such a way as to reduce the likelihood that they will occur and the magnitude of any problems that do ensue.

14.5 PRESCRIPTION FORMULATION

14.5.1 Calculation of Energy Requirements

Evidence suggests that while critically ill patients are in a catabolic state their energy needs are not necessarily 59
increased above normal.[5,6] Furthermore, excessive calories and nutrients in the form of PN can have adverse 60
consequences including many of the metabolic complications described in Table 14-1, as well as fatty infiltration of the liver and hypercapnia.[7] For these reasons, caloric goals for parenterally fed patients should be conservative and, in most cases, based on an estimate of a patient's resting energy expenditure ($70BW_{kg}^{0.75}$; see Chapter 13, Enteral Nutrition). The caloric goal can then be adjusted based on the patient's response.

Table 14-1 Conditions Predisposing Patients Receiving PN to Metabolic Complications

Complication	**Predisposing Conditions**
Hyperglycemia	Diabetes mellitus, hyperadrenocorticism
Lipemia	Pancreatitis, idiopathic hyperlipidemia, diabetes mellitus, hyperadrenocorticism
Azotemia	Renal failure
Hyperammonemia	Hepatic failure, portosystemic shunt
Refeeding syndrome (hypokalemia, hypophosphatemia, or hypomagnesemia)	Prolonged starvation or catabolic disease, diabetes mellitus

PN, Parenteral nutrition.

14.5.2 Calculation of Protein Requirements

There has been limited investigation of the protein requirements of companion animals receiving PN.[7,8] Most recommendations call for 4 to 6 g of protein per 100 kcal for dogs and 6 g or more of protein per 100 kcal for cats. Some clinicians advocate meeting the patient's energy requirements with nonprotein calories from dextrose and lipids in addition to providing the required protein. This approach has the potential of providing excessive calories, particularly in patients deemed to have high protein requirements. A more conservative approach is to subtract the required protein calories from the patient's total energy requirement and provide the balance as nonprotein calories. Using the recommendations given above, this roughly translates into 15% to 25% of calories for dogs and 25% to 35% of calories for cats delivered as protein. Patients that are protein depleted or have high ongoing losses will require PN admixtures containing protein amounts in the upper ranges. For patients with conditions that impair protein tolerance, it may be necessary to restrict the amount of protein in the PN admixture below the lower end of these ranges.

Amino acid solutions are available in concentrations ranging from 3% to 15%. Because of increasing osmolarity, solutions more concentrated than 6% should not be used for peripherally infused PN. The electrolyte content of these products varies. Because the less concentrated products are used for peripherally infused PN, they often have higher concentrations of electrolytes to preclude the need for further supplementation. The more concentrated solutions can be obtained with or without additional electrolytes. Using the amino acid solutions without supplements for PN formulation and providing electrolytes in the patient's IV fluids allows greater flexibility.

14.5.3 Calculation of Lipid and Carbohydrate Requirements

Once the percentage of protein calories has been established, it is necessary to decide how to apportion the remaining calories between carbohydrate and fat. Although it is possible to provide all nonprotein calories as carbohydrate using dextrose solutions, lipid emulsions have the advantage of being isoosmolar and a more concentrated form of calories. Also, patients are at greater risk of becoming hyperglycemic when fed PN admixtures containing large amounts of dextrose. This is especially a concern in cats.[2] Therefore, unless there is a preexisting condition that would suggest fat intolerance, lipid emulsions can be used to provide 50% to 70% of the nonprotein calories, with the balance delivered as dextrose.

Lipid emulsions are available in 10% (1.1 kcal/ml), 20% (2.0 kcal/ml), and 30% (3.0 kcal/ml) concentrations. They are composed of emulsified soybean or safflower oils with a particle size equivalent to a chylomicron. Dextrose is available in concentrations ranging from 5% to 70%. For centrally infused PN, 50% dextrose (1.7 kcal/ml, 2500 mOsm/L) is typically used. For peripherally infused PN it is necessary to use lower concentrations (e.g., 10%, 0.34 kcal/ml, 500 mOsm/L; or 20%, 0.68 kcal/ml, 1000 mOsm/L) due to osmolarity issues.

14.5.4 Calculation of Micronutrient Requirements

Although parenteral forms of all essential micronutrients are available, typically only injectable B complex and certain electrolytes (phosphorus and magnesium) are included in PN admixtures that are used for companion animals. Some clinicians also add trace element preparations containing zinc, because there is evidence that this nutrient can be depleted rapidly in critically ill patients.[9] Table 14-2 contains dosage guidelines for these nutrients and Box 14-1 contains a sample prescription formulation.

14.6 DELIVERY AND MONITORING

A patient starting PN should receive 50% of goal nutrients the first day as a constant rate infusion over 24 hours and, if that is well tolerated, can receive 100% of its goal the following day. The PN admixture should be delivered via a dedicated catheter or port of a multilumen catheter using a 1.2-μm filter (to prevent lipid embolization) and a fluid pump. The PN admixture should be disconnected only when changing the bottle or bag, and the administration set should also be changed at that time. Gloves should be worn in performing catheter care and changing bottles and administration sets. Ideally patients should be weaned off PN over the course of several hours once they are receiving at least 50% of their goal calories through voluntary intake or enteral feeding. If it becomes necessary to abruptly discontinue PN, 5% dextrose should be added to the patient's IV fluids to prevent hypoglycemia.

Monitoring of patients receiving nutritional support has been reviewed in Chapter 13, Enteral Nutrition. For patients receiving parenteral nutritional support, particular attention should be paid to the catheter site for signs of phlebitis or infection. Hydration status and fluid tolerance should be assessed regularly. Blood glucose, serum sodium, and 60 61 potassium concentrations should be monitored at least once daily. Insulin administration may be indicated if persistent hyperglycemia occurs (0.1 U/kg regular insulin IV, IM, or SC as needed; continuous infusion by IV may be necessary in severely affected animals). Whenever a packed cell volume determination is performed, the hematocrit tube should be examined for evidence of lipemia. Serum phosphorus and magnesium concentrations should be checked after the first day of PN infusion. If serum levels of these electrolytes have decreased significantly, further monitoring is warranted so that patients can receive appropriate supplementation if necessary. Complete blood counts and serum chemistry analysis should be performed as indicated, but at least once weekly while patients are receiving PN. Ammonia levels may be indicated in animals with hepatic insufficiency or hepatic encephalopathy.

Table 14-2 Guidelines for Micronutrient Dosages in PN Admixtures

Micronutrient	**Dosage**
Vitamin B complex*	0.2 to 0.5 ml/100 kcal
Potassium phosphate	8 to 10 mmol/1000 kcal
Magnesium sulfate	0.8 to 1.0 mEq/100 kcal
Zinc	1 μg/kcal

PN, Parenteral nutrition.

* Injectable vitamin B complex does not contain folate because of compatibility issues; thus patients receiving PN for more than a few days may become deficient and should be supplemented with this nutrient via a route other than the PN admixture.

14.7 PREVENTING AND MANAGING COMPLICATIONS

14.7.1 Catheter and Parenteral Nutrition Admixture Complications

Catheter complications include loss of vascular access due to catheter malposition, thrombosis, thrombophlebitis, or catheter-associated infection. The incidence of complications can be reduced greatly with appropriate catheter selection and adherence to strict guidelines for catheter care.

Complications involving the PN admixture include microbial contamination, precipitation of admixture components, and drug-nutrient interactions. These problems can be avoided by proper compounding of the admixture under sterile conditions and infusion of the admixture through a dedicated line. The particles making up a lipid emulsion can come out of suspension in an improperly compounded admixture. Lipid-containing admixtures should be inspected periodically during infusion for signs of separation or layering. An in-line filter will prevent fat embolism in patients receiving lipid-containing PN.

14.7.2 Metabolic Complications

Most metabolic complications can be anticipated based on the patient's nutritional assessment, and can be avoided or minimized by formulating the PN admixture accordingly. Most metabolic disturbances are less likely to occur if estimates of caloric needs are conservative. “Refeeding syndrome” (see Chapter 13, Enteral Nutrition) has been described in patients receiving PN.[1,2] Those at increased risk of the electrolyte abnormalities seen with this condition are patients that have experienced a period of prolonged starvation or catabolism or patients with uncontrolled diabetes mellitus. In correcting electrolyte abnormalities, supplementation in the IV fluids as opposed to the PN admixture allows greater flexibility. Once the amount of electrolyte supplementation for maintenance is established, it can be included in the PN formulation.

14.7.2.1 Box 14-1 Centrally Administered PN Example: High-Protein Formulation for a Cat

Weight: 4.5 kg RER = 216 kcal/day

Day 1 Goal: 50% RER = (0.5)(216) = 108 kcal

Day 2 Goal: 100% RER = 216 kcal

Protein Calories

30% from amino acids

Nonprotein Calories

70% from lipid

30% from dextrose

Solutions

8.5% amino acids (without electrolytes)

50% dextrose

20% lipid emulsion

Trace element solution containing 0.8 mg zinc/ml

Potassium phosphate (3 mmol/ml)

Injectable vitamin B complex

14.7.2.1.1 Day 1 Calculations

1 Amino acids

(0.3)(108 kcal) = 32 kcal from protein

There are 4 kcal/g in protein

Therefore you need 8 g of protein (32 kcal ÷ 4 kcal/g = 8 g)

8.5% amino acid solution = 0.085 g protein/ml

Therefore you need 94 ml of 8.5% amino acid solution (X ml = 8 g ÷ 0.085 g/ml)

2 Nonprotein calories

(0.7)(108 kcal) = 76 kcal

(a) 50% dextrose to provide 30% nonprotein calories = 23 kcal

50% dextrose solution = 1.7 kcal/ml

Therefore you need 13 ml 50% dextrose solution (X ml = 23 kcal ÷ 1.7 kcal/ml)

(b) 20% lipid emulsion to provide 70% nonprotein calories = 53 kcal

20% lipid emulsion = 2 kcal/ml

Therefore you need 27 ml 20% lipid emulsion (X ml = 53 kcal ÷ 2.0 kcal/ml)

3 Trace elements

Zinc prescribed at 1 μg/kcal delivered

Trace element solution contains zinc 0.8 mg/ml

Therefore you need 0.14 ml of trace element solution (X ml = 108 kcal ÷ [0.8 mg/ml × 1000])

4 Potassium phosphate

Prescribed at 8 mmol/1000 kcal delivered

Therefore you need 0.9 mmol potassium phosphate (X mmol = [8 mmol × 108 kcal] ÷ 1000 kcal)

Potassium phosphate solution = 3 mmol/ml

Therefore you need 0.3 ml potassium phosphate (X ml = 0.9 mmol ÷ 3 mmol/ml)

5 Vitamin B complex

Prescribed at 0.2 ml/100 kcal delivered

Therefore you need 0.2 ml vitamin B complex (X ml = [0.2 ml × 108 kcal] ÷ 100 kcal)

6 Infusion rate

135 ml/24 hr = 5.6 ml/h

r

14.7.2.1.2

Day 2 Calculations

Same as for Day 1—just substitute 216 kcal for 108 kcal

14.8

SUGGESTED FURTHER READING*

E O'Toole, CW Miller, BA Wilson, et al.: Comparison of the standard predictive equation for calculation of resting energy expenditure with indirect calorimetry in hospitalized and healthy dogs. *J Am Vet Med Assoc*. **225**, 2004, 58, *Prospective investigation of the energy requirements of hospitalized dogs*.

SC Pyle, SL Marks, PH Kass: Evaluation of complications and prognostic factors associated with administration of total parenteral nutrition in cats: 75 cases (1994-2001). *J Am Vet Med Assoc*. **225**, 2004, 242, *Comprehensive retrospective investigation of the use of PN in cats*.

JD Reuter, SL Marks, QR Rogers, TB Farver: Use of total parenteral nutrition in dogs: 209 cases (1988-1995). *J Vet Emerg Crit Care*. **8**, 1996, 210, *Comprehensive retrospective investigation of the use of PN in dogs*.

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* See the CD-ROM for a complete list of references

15 Chapter 15 Respiratory Failure

Linda Barton, DVM, DACVECC

15.1 KEY POINTS

- Respiratory failure is conventionally defined as an arterial partial pressure of oxygen (PaO_2) of less than 60 mm Hg on a fractional concentration of inspired gas (FiO_2) of less than 0.5 or an arterial partial pressure of carbon dioxide ($PaCO_2$) of more than 50 mm Hg.
- Respiratory failure can be categorized as hypercapnic pump failure or hypoxemic lung failure.
- Failure of the lung leads to hypoxemia with normocapnia or hypocapnia.
- Failure of the ventilatory pump results in alveolar hypoventilation, hypercapnia, and mild oxygen-responsive hypoxemia.
- Respiratory muscle fatigue, caused by an imbalance between respiratory muscle energy demands and energy supply, contributes to ventilatory failure in patients with respiratory disease.
- If the underlying cause is not readily reversible, patients with respiratory failure require mechanical ventilation until the cause can be identified and treated.

15.2 INTRODUCTION

The primary function of the respiratory system is the oxygenation of, and elimination of, carbon dioxide from the mixed venous blood. The two major components of the respiratory system are the lung (the gas exchange organ) and the respiratory muscles (the pump that ventilates the lung); each contributes to the performance of this gas exchange function. Disease leading to dysfunction of either of these two components can result in respiratory failure.

Inadequacy of gas exchange is reflected in the patient's blood gas values. Respiratory failure is conventionally defined as a partial arterial pressure of oxygen (PaO_2) of less than 60 mm Hg on a fractional concentration of oxygen in inspired gas (FiO_2) of over 0.5 or an arterial partial pressure of carbondioxide ($PaCO_2$) of more than 50 mm Hg.[1] Clinical signs of impending or existing respiratory failure include an increasing respiratory rate and increased work of breathing as evidenced by the use of accessory muscles of ventilation, and assumption of abnormal body postures.

Failure of each part of the respiratory system results in a distinct clinical picture (Box 15-1). Failure of the ventilatory pump results in alveolar hypoventilation and hypercapnia. Mild oxygen-responsive hypoxemia is seen in hypoventilating patients; however, the hallmark of ventilatory failure is an elevation in $PaCO_2$. In contrast, failure of the lung leads to hypoxemia with normocapnia or hypocapnia. In hypoxemic respiratory failure, the $PaCO_2$ remains normal or decreased because hypoxemia stimulates the ventilatory drive.

Although discussed as separate entities, both types of respiratory failure can coexist in a patient. Most of the lung diseases that lead to hypoxemia also increase the work of breathing and therefore the energy demands of the respiratory muscles. Hypoxia itself decreases the amount of energy available to the respiratory muscles, predisposing them to fatigue. In patients with severe or persistent lung failure, the increased ventilatory demands can exceed ventilatory capacity leading to pump failure secondary to respiratory muscle fatigue.[2]

15.2.1

Box 15-1 Disorders Predisposing to Respiratory Failure

15.2.1.1

Hypercapnic Pump Failure

15.2.1.1.1

Disorders of CNS Respiratory Centers

Overdose of respiratory depressant drugs (sedative, narcotics)

Intracranial disease

Head trauma

15.2.1.1.2

Neuromuscular Disorders

Cervical myelopathies

Myasthenia gravis

Botulism

Organophosphate toxicity

Polyradiculoneuritis

Phrenic nerve injury

Electrolyte disorders (hypophosphatemia, hypomagnesemia)

Severe malnutrition

Respiratory muscle fatigue

15.2.1.1.3

Disorders of Chest Wall and Pleural Function

Flail chest

Pleural effusion

Pneumothorax

Hemothorax

Kyphoscoliosis

Contracted scars over thorax

15.2.1.1.4 Disorders of the Conducting Airways

Laryngeal paralysis

Laryngeal edema

Asthma

Bronchospasm

15.2.1.2 Hypoxemic Lung Failure

Pulmonary contusion

Pneumonia

Pulmonary edema (cardiogenic, noncardiogenic)

Pulmonary thromboembolism

Pulmonary hemorrhage

Aspiration

Smoke inhalation

Near drowning

Interstitial lung disease

CNS, Central nervous system.

15.3 HYPOXEMIC RESPIRATORY FAILURE

Hypoxemic respiratory (lung) failure occurs secondary to a variety of disease processes that interfere with gas exchange at the alveolar level (see Box 15-1). Any of the four pathophysiologic mechanisms of hypoxemia—hypoventilation diffusion impairment, shunt, and ventilation-perfusion mismatch—can contribute to the hypoxemia seen in patients with lung failure. However, mismatch of ventilation and perfusion is the most important cause.[3]

The ratio of alveolar ventilation (V) to pulmonary blood flow (Q) determines the composition of gas leaving the lung. The lung is divided into a large number of gas exchange units, each composed of an alveolus and its associated pulmonary capillary. Ideally the volume of alveolar gas presented to the blood-gas barrier at each gas exchange unit would be matched by the volume of blood perfusing the unit, resulting in a V/Q ratio of 1.0 and complete equilibration of oxygen between the alveolar gas and the pulmonary capillary. In the normal lung, regional differences in ventilation and perfusion result in a small amount of V/Q inequality. Disease processes resulting in lung failure cause marked disturbances in the V/Q ratio, abnormal gas exchange, and hypoxemia.[4]

Pulmonary capillary blood flow in excess of alveolar ventilation produces low V/Q units. The partial pressure of oxygen (PO_2) in the effluent blood of these gas exchange units is low (approaching the PO_2 of mixed venous blood) and causes arterial hypoxemia. Low V/Q units are termed *venous admixture* or *shunt effect* and develop when there is decreased ventilation to normally perfused regions of the lung, or when there are areas in the lung with a greater reduction in ventilation than in perfusion. Venous admixture occurs with disease processes that cause the alveoli to fill with water (cardiogenic edema, noncardiogenic edema), pus (pneumonia), blood (trauma, coagulopathy), or cells (neoplasia). Bronchospasm also produces venous admixture. Zero V/Q units, or true shunt, occurs when blood enters the left side of the heart without respiring with alveolar gas. Normally a small amount of blood bypasses the lung via the bronchial, pleural, and thebesian veins; this is referred to as *anatomic shunt*. Pathologic capillary shunt occurs when blood traverses the pulmonary capillaries but does not respire with alveolar gas. Capillary shunt occurs in regions of the lung that are atelectatic or completely consolidated.[5,6]

Any part of the tidal volume that does not participate in gas exchange is referred to as *dead space*. Anatomic dead space is the amount of air in the conducting airways. Physiologic dead space occurs when the blood flow to ventilated alveoli is reduced or absent. Causes of physiologic dead space include pulmonary vascular obstruction (pulmonary thromboembolism, heartworm disease, disease processes associated with damaged capillaries and intravascular coagulation such as sepsis, systemic inflammatory response syndrome), decreased pulmonary perfusion (hypovolemia, low cardiac output, pulmonary hypertension), and overdistention of alveoli caused by mechanical ventilation with high tidal volumes or pressures.

Diffusion impairment is an uncommon cause of lung failure. Diffusion of oxygen across the alveolar-capillary membrane is affected by the total surface area of the membrane, the thickness of the diffusion barrier, the diffusion coefficient of the gas, and the pressure gradient of the gas across the membrane. In the normal lung, the alveolar-capillary surface is extensive and very thin, supporting efficient gas exchange and providing a large reserve capacity for diffusion. Complete equilibration between the PO_2 in the pulmonary capillary blood and the alveolar gas usually occurs by the time a red blood cell has traveled only one third of the way along the capillary. Disease processes that decrease the surface area of the alveolar-capillary membrane (emphysema, lung lobectomy) or increase the thickness of the diffusion barrier (pulmonary edema, diffuse interstitial fibrosis, interstitial pneumonia) may adversely affect diffusion but must be severe to exhaust the large reserve capacity. Any hypoxemia caused by diffusion impairment can be readily corrected with oxygen administration. Increasing the inspired concentration of oxygen increases the alveolar PO_2 and therefore the pressure gradient driving the diffusion of oxygen across the abnormal diffusion barrier.[4]

15.4 HYPERCAPNIC RESPIRATORY FAILURE

The lung is ventilated by the respiratory pump. The pump consists of the respiratory controllers in the central nervous system, the pathways that connect the central controllers with the respiratory muscles (spinal cord, peripheral nerves, and neuromuscular junction), and the chest wall and associated respiratory muscles. Disorders of any of these pump components can result in the inability to sustain adequate ventilation and hypercapnic respiratory failure (see Box 15-1). Diseases of the airways can also adversely affect ventilation. Disorders such as asthma and laryngeal dysfunction cause a reduction in airway diameter, an increase in airway resistance, and a decreased flow of gas into the lungs.

In addition to disorders causing decreased central respiratory drive, impairment of neuromuscular transmission, mechanical defects in the ribcage, and a marked increase in airway resistance, hypercapnic ventilatory failure may occur secondary to respiratory muscle fatigue. Fatigue is defined as the inability of the respiratory muscles to continue to generate sufficient pressure to maintain alveolar ventilation and a normal $PaCO_2$.[3] Initiation of a spontaneous breath requires the inspiratory muscles to generate sufficient force to overcome the elastic (lung compliance) and inelastic (resistance) load of the lungs and chest wall. In health, the ventilatory capacity (the amount of mechanical work that the respiratory muscles can perform) greatly exceeds the demand (the load imposed on the respiratory muscles). Respiratory muscle fatigue occurs when the energy supply to the muscles is insufficient to meet energy demands (Figure 15-1).

Energy demands are determined by the work of breathing and the strength and efficiency of the inspiratory muscles. Respiratory diseases that cause hypoxemia are usually characterized by abnormal lung mechanics and an increased work of breathing. Decreased compliance is caused by diseases such as acute respiratory distress syndrome, pneumonia, pulmonary edema, and pulmonary fibrosis. Bronchoconstriction, increased airway secretions, and bronchial mucosal edema cause an increase in the resistance forces. Muscle efficiency, the ratio of work performed to energy consumed, is decreased in diseases associated with hyperinflation, such as asthma. With hyperinflation, both the diaphragm and intercostal muscles work at a short length, an inefficient part of their force-length relationship.[2,3]

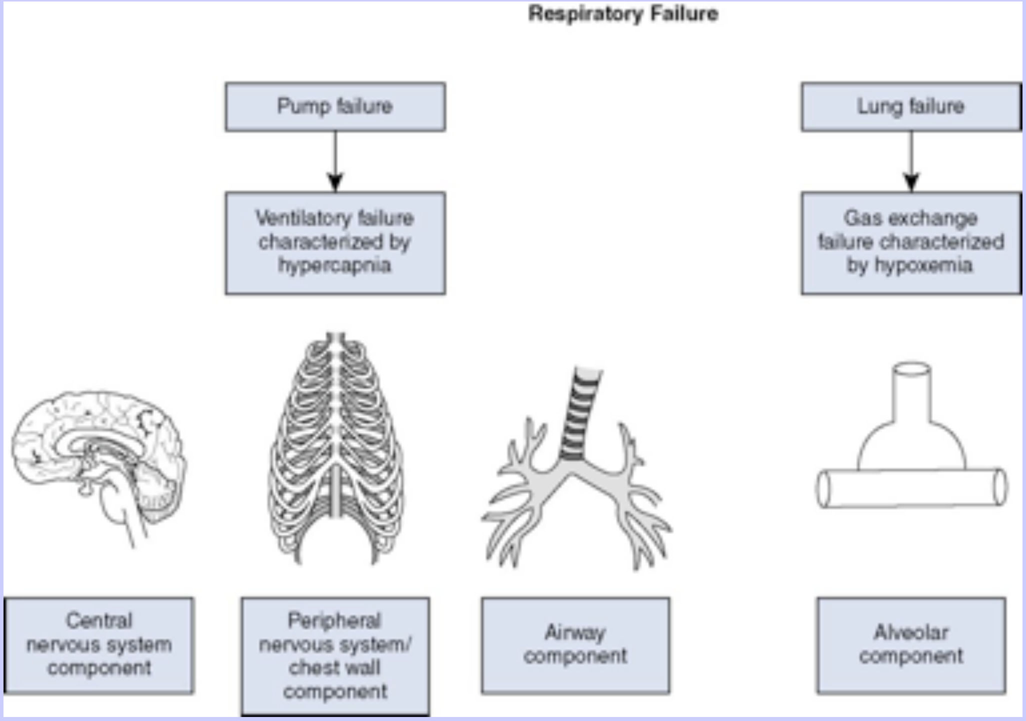
Concurrent with increased energy demands, patients with lung disease often have a decrease in respiratory muscle energy supply. Factors affecting the supply of energy to the respiratory muscles are blood flow to the muscles and the concentration of oxygen and other blood substrates (glucose, free fatty acids) in the blood. Arterial oxygen concentration is decreased with anemia, dysfunctional hemoglobin, and hypoxemia. In addition to adequate oxygen delivery, the muscles must be able to utilize the delivered oxygen. In sepsis and cyanide poisoning there is an inability of the cells to extract and use oxygen. Blood flow to muscles can be decreased in low cardiac output states. Blood flow to muscles is decreased during strenuous inspiratory efforts. Forceful muscle contractions cause compression of intramuscular vessels, limiting nutrient blood flow. Because blood flow occurs only during expiration, prolonged inspiration also causes decreased blood flow. Malnutrition and catabolic states can cause depletion of glycogen and other energy stores, predisposing to muscle fatigue.[2]

When respiratory muscle energy demand exceeds supply, fatigue develops. Decreased ability of the muscles to generate sufficient force for normal expansion of the thorax ensues, resulting in a decreased tidal volume, decreased alveolar ventilation, and hypercapnia. Evidence suggests that when fatiguing loads are imposed on the respiratory muscles, reflex changes in the central respiratory drive cause a rapid, shallow breathing pattern. The resultant smaller tidal volume reduces the energy demands per breath, a strategy that may save energy and avoid complete exhaustion at the expense of alveolar hypoventilation and hypercapnia.[2,3]

15.5 TREATMENT

All patients in respiratory distress should receive supplemental oxygen. Pulse oximetry and PaO_2, $PaCO_2$, and $PvCO_2$ monitoring can be used to further evaluate the patient's oxygenation and ventilatory status. Hypoxemia caused by hypoventilation, diffusion impairment, and low V/Q units (shunt effect) will improve with oxygen supplementation. Oxygen administration will not result in an increase in PaO_2 in true capillary shunt (zero V/Q) units. The blood passing through those units never interfaces with alveolar gas and therefore is not oxygenated. Because of the sigmoidal shape of the hemoglobin saturation curve, increasing the PO_2 to those alveoli that are well ventilated does not help improve the oxygenation of the blood leaving the lung. The hemoglobin molecules traversing these alveoli are already carrying their maximum capacity of oxygen, and increasing the amount of oxygen dissolved in the blood does not significantly increase the oxygen content.[4] Supplemental oxygen will reverse the hypoxemia caused by hypoventilation, but the hypercapnia will persist until the underlying cause of the hypoventilation is corrected.

Figure 15-1 Respiratory muscles fatigue if the energy demands exceed the energy supplied to the muscles.


Respiratory Failure
Pump failure
Lung failure
Ventilatory failure characterized by hypercapnia
Gas exchange failure characterized by hypoxemia
Central nervous system component
Peripheral nervous system/ chest wall component
Airway component
Alveolar component

If the cause of the respiratory failure cannot quickly be identified and reversed (e.g., evacuate the pneumothorax, reverse the narcotic sedative), the patient should be intubated and ventilated while the underlying cause is evaluated. Mechanical ventilation does not correct the underlying disorder. It only supports the respiratory system until the appropriate therapies can be applied. Returning the patient to health requires identification and treatment of the underlying pathology.

15.6 SUGGESTED FURTHER READING*

LNB Pierce: Mechanical ventilation: indications, basic principles of ventilator performance of the respiratory cycle, and initiation. In LNB Pierce (Ed.): *Guide to mechanical ventilation and intensive respiratory care*. 1995, Saunders, Philadelphia, *This chapter includes a discussion of the definition, classification, and causes of acute respiratory failure. Also included is an overview of the physiology of mechanical ventilation compared with spontaneous ventilation and recommended initial ventilator settings*. 66

67 C Roussos, A Koutsoukou: Respiratory failure. *Eur Respir J*. **22**, 2003, 3S, *This article discusses respiratory failure, with particular emphasis on the adaptations in respiratory muscles and central respiratory controllers that lead to hypercapnia in chronic respiratory disease*.

BA Shapiro, WT Peruzzi, R Templin: Assessment of the lung as an oxygenator. In JF Shannahan (Ed.): *Clinical application of blood gases*. 1994, Mosby, St Louis, *This chapter discusses the derivation of the classic shunt equation and discusses advantages and disadvantages of methods used to estimate the shunt fraction in patients without a pulmonary artery catheter*.

JB West: In *Respiratory physiology: the essentials*. ed 7, 2005, Lippincott Williams & Wilkins, Baltimore, *This textbook of basic respiratory physiology is easy to read and includes many useful illustrations*.

* See the CD-ROM for a complete list of references.

16 Chapter 16 Upper Airway Disease

Merilee F. Costello, DVM, DACVECC

16.1 KEY POINTS

- Upper airway disease is a common cause of respiratory distress in veterinary medicine.
- Rapid identification, intervention, and stabilization is essential to minimize complications.
- Diagnostic tests for evaluating patients with upper airway disease include radiography, laryngeal examination, flexible endoscopy, bronchoscopy, biopsy, endotracheal wash, and computed tomography.
- Emergency treatment for an animal with upper airway disease consists of minimizing stress, providing oxygen therapy, external cooling if necessary, and antiinflammatory therapy if indicated.
- Definitive management is variable depending on the underlying cause of the upper airway disease.
- Systemic sequelae to upper airway disease include aspiration pneumonia, noncardiogenic pulmonary edema, and heatstroke.
- The prognosis for animals with upper airway disease is variable depending on the underlying cause, the severity, and the other systems affected.

16.2 INTRODUCTION

Upper airway disease and obstruction is a common cause of morbidity in veterinary medicine, and this is particularly true in the emergency and critical care settings. There are numerous causes of upper airway disease, and the clinical signs are variable. It is important to remember that any abnormality of the upper airway will impair the natural defenses of the airway and may predispose the patient to pulmonary parenchymal diseases such as aspiration pneumonia and noncardiogenic pulmonary edema. Rapid identification, stabilization, diagnosis, and definitive therapy are imperative to minimize the morbidity and mortality that can be associated with upper airway disease.

16.3 CLINICAL SIGNS

The clinical signs in affected patients will vary based on species, underlying etiology, chronicity, comorbid conditions, and severity of the airway obstruction. Animals can exhibit variable degrees of dyspnea and respiratory distress. In mildly affected animals, clinical signs may include a change in voice, gagging or retching, stertor, stridor, or a dry, unproductive cough. Stertor is a low-pitched snoring sound that is generally associated with obstructive diseases affecting the nasal passages or nasopharynx. In contrast, stridor is a higher pitched respiratory noise that is generally heard during the inspiratory phase of respiration with extrathoracic obstruction and is associated with diseases affecting the larynx or trachea.[1,2] The upper airway noise in these patients often increases as the severity of the obstruction progresses. Open-mouth breathing will alleviate the airway obstruction if the disease is affecting only the nasal passages or nasopharynx. Although panting is common in dogs, open-mouth breathing in cats is never normal and should alert the clinician to the presence of respiratory disease.

Hyperthermia is a common clinical sign in dogs with upper airway disease. This occurs less frequently in feline patients, likely due to their more sedentary lifestyle. Panting is one of the primary mechanisms of thermoregulation in animals; the movement of fresh air through the upper airway effectively increases heat loss through evaporation.[3,4] In animals with upper airway disease, this air movement is compromised, predisposing them to hyperthermia. This hyperthermia can be extreme, and aggressive cooling may be necessary in severely affected patients (see Chapter 167, Heatstroke).[5]

Auscultation often reveals significant referred upper airway noise. The increased noise can be better localized by auscultating over the larynx and trachea, as well as the thorax. Inspiratory dyspnea with stertor or stridor typically results from extrathoracic obstructive diseases, and intrathoracic airway obstruction more commonly leads to expiratory dyspnea with adventitious sounds. Careful attention should be paid to thoracic auscultation to identify concurrent pulmonary parenchymal disease.

In animals with significant upper airway obstruction, severe respiratory distress and cyanosis can occur. These patients may show severe clinical signs such as an orthopneic stance when breathing, severe stridor, coughing, gasping, retching or vomiting, or collapse. In these cases, immediate anesthesia and intubation (or a tracheostomy) are imperative to minimize morbidity and mortality.

16.4 EMERGENCY STABILIZATION

Although treatment varies depending on the underlying disease process, the general emergency approach is similar in all patients with upper airway disease. As previously mentioned, these animals are fragile and can decompensate quickly, so any additional stress can be life threatening and will lead to an increase in oxygen requirements and therefore respiratory rate. This increased respiratory rate will only further exacerbate upper airway dysfunction. Early stabilization often relies on the administration of anxiolytics and sedatives (see Chapter 162, Sedation of the Critically Ill Patient). These agents should be given IM initially if the patient is not stable enough to undergo the stress of placing an IV catheter.

Acepromazine can be administered at a dosage of 0.005 to 0.05 mg/kg IV, IM, or SC. This is an excellent sedative, but it is important to remember that vasodilation and hypotension can occur, so it should be reserved for patients that are hemodynamically stable. Butorphanol is a sedative and antitussive, which can be used as a single agent or in combination with acepromazine. The dosage of butorphanol is 0.1 to 0.6 mg/kg IM, IV, or SC. In addition to sedation, patients should be placed in an oxygen-rich environment. Short-acting glucocorticoids have been recommended to reduce laryngeal and tracheal inflammation, edema, and swelling. Dexamethasone sodium phosphate at a dosage of 0.2 to 0.4 mg/kg can be administered IV, IM, or SC. In cases of suspected neoplasia, steroids should be avoided because this can complicate the diagnostic interpretation.

In patients with an elevated temperature, external cooling methods should be instituted. If sedation and oxygen therapy, with or without steroid therapy, fails to stabilize the patient, intubation is indicated. In the rare case in which intubation is not possible, an emergency tracheostomy should be performed to achieve a patent airway (see Chapter 18, Tracheostomy). When an emergency tracheostomy is not feasible, a small catheter may be passed into the trachea through the mouth or between tracheal rings and high-pressure jet ventilation or repetitive oxygen boluses from an anesthesia oxygen flow valve may be delivered until a tracheostomy is performed.

16.5 DIAGNOSTICS

Numerous disease processes can affect the upper respiratory tract. Differentiating the underlying cause in an individual patient can be challenging because the clinical signs are not pathognomonic for any single cause. Signalment, breed, history, and physical examination can often provide some information, but a detailed and thorough diagnostic approach is necessary to fully evaluate the anatomy and function of the upper airway. Even mild stress in animals with upper respiratory tract obstruction can be life threatening. In patients with mild clinical signs, less invasive testing may be possible with little or no sedation. In contrast, patients with moderate or severe airway compromise often require heavy sedation and intubation for diagnostic evaluation. In any case, the clinician should always be prepared to gain control of the airway, either via intubation or emergency tracheostomy, if necessary.

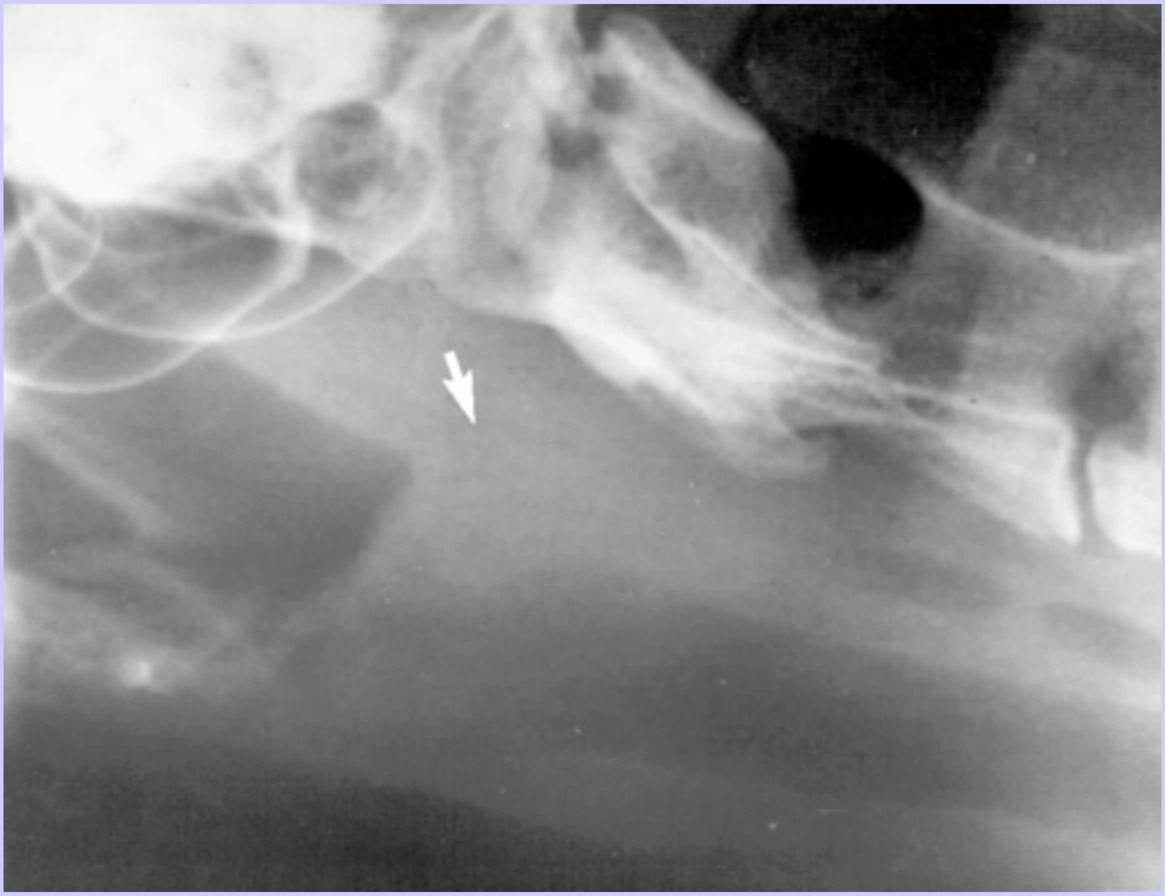
Although rarely diagnostic for a specific cause of upper airway disease, radiographs are important for evaluating both the upper and lower respiratory tracts. One ventrodorsal and two lateral views of the thorax should be taken to evaluate for metastatic disease, aspiration pneumonia, or noncardiogenic pulmonary edema. Thoracic radiographs are also used to evaluate the trachea and look for intrathoracic masses. Cervical radiographs may show evidence of laryngeal or pharyngeal neoplasia (Figure 16-1), radiodense foreign bodies, or extramural masses causing compression of the larynx or trachea. In patients with nasal or nasopharyngeal disease, skull radiographs (or computed tomography) may be indicated to evaluate the nasopharynx, the bullae, and the external canal and petrous temple bone. Unlike thoracic and cervical radiographs, patients undergoing skull radiography require general anesthesia for proper radiographic positioning.

Laryngeal examination is an essential part of the diagnostic evaluation in any patient with clinical signs attributable to upper airway disease. The laryngeal examination is used to evaluate the function and movement of the rima glottidis, including the vocal cords and arytenoid cartilages. The larynx is visualized to assess for thickening or irregularities, and the soft palate and laryngeal saccules should be identified and evaluated.

After evaluation of the upper respiratory tract, an endotracheal wash should be considered, particularly in any patient with signs of lower airway disease. The patient should be intubated with a sterile endotracheal tube and sterile saline aliquots (3 to 5 ml for cats; 5 to 7 ml for dogs) are injected into the endotracheal tube through a sterile red rubber catheter. The patient is given gentle coupage and the fluid suctioned via the red rubber catheter or a sterile suction catheter. The fluid obtained should be submitted to a diagnostic laboratory for fluid analysis and bacterial culture and sensitivity. Additional cultures may be indicated based on cytologic findings.

Endoscopy is required for evaluation of the upper airway caudal to the epiglottis. Endoscopy is used to identify nasopharyngeal stenosis, nasopharyngeal abscesses or masses, nasopharyngeal polyps, or extramural compression. 68
The endoscope can be retroflexed to evaluate the caudal nasal cavity. Finally, tracheoscopy is helpful in evaluating 69
for tracheal collapse, tracheal tumors, extramural compression, or tracheal foreign bodies.

Figure 16-1 Lateral cervical radiograph depicting a mass effect in the laryngeal region. From Costello MF, Keith D, Hendrick M, King L: Acute upper airway obstruction due to inflammatory laryngeal disease in 5 cats, *J Vet Emerg Crit Care* 11:205-210, 2001.



In cases with an irregularity, thickening, or mass effect associated with the larynx or pharynx identified on laryngeal examination, biopsy is always required for a definitive diagnosis because neoplasia and inflammatory disease are indistinguishable on gross examination.

Computed tomography of the skull can be an invaluable diagnostic test for nasal and nasopharyngeal disease. Although it cannot be used for functional abnormalities such as laryngeal paralysis, it is an excellent tool for evaluating the nasal and nasopharyngeal area for tumors or osteolysis, polyps, abscesses, stenosis, or collapse. As with skull radiographs, general anesthesia is required for adequate positioning and to avoid movement artifacts.

16.6 DISEASES OF THE UPPER AIRWAY

16.6.1 Laryngeal Paralysis

Laryngeal paralysis is a common cause of upper airway obstruction in dogs. Middle-aged to older, large to giant breed dogs are most often affected, and most studies have found that a higher number of male dogs are affected.[6-8] In normal dogs, innervation of the cricoarytenoideus dorsalis muscle by the recurrent laryngeal nerve allows the animal to abduct the arytenoid cartilage during inspiration. In animals with laryngeal paralysis, there is denervation of the recurrent laryngeal nerve resulting in cricoarytenoideus dorsalis muscle atrophy. This atrophy prevents the animal from abducting the arytenoid cartilage and results in narrowing of the glottic lumen and subsequent upper airway obstruction. In some breeds, such as Bouvier des Flandres, Siberian Husky, Dalmatian, Rottweiler, and Bull Terrier, this denervation may be congenital.[6-8] Other underlying causes include trauma; diffuse neuromuscular disease such as myasthenia gravis, polyneuropathy, or polymyopathy; neoplasia; and hypothyroidism. Unfortunately, however, in most cases an underlying cause is never identified. These cases are referred to as *idiopathic laryngeal paralysis*.

Clinical signs are consistent with upper airway disease and include inspiratory stridor, decreased activity and exercise intolerance, ptyalism, and voice change. Severely affected animals may show signs of upper airway obstruction including cyanosis, gagging, retching, and collapse.

In most cases, diagnosis is made by direct visualization of the arytenoid cartilages during laryngeal examination or via laryngoscopy. Laryngeal examination requires anesthesia, and this can sometimes confound evaluation of laryngeal function, which may be altered by many anesthetic drugs. In a study evaluating the effects of various anesthetic combinations on laryngeal function in normal dogs, IV thiopental given to effect had the least effect on laryngeal function. In addition, acepromazine combined with thiopental or propofol, and ketamine combined with diazepam, were not recommended because some of the normal dogs had no detectable arytenoid cartilage movement when anesthetized with these drugs.[9] Doxapram may facilitate the diagnosis of laryngeal paralysis in dogs that are not breathing well after induction.[10]

Transnasal laryngoscopy with a 2.5-mm flexible endoscope enabled researchers to differentiate normal laryngeal function in three dogs and abnormal laryngeal function in four dogs without anesthesia.[11] Two of the dogs required mechanical stimulation of the laryngeal mucosa for complete evaluation. Nevertheless, this may be a useful diagnostic technique.

Medical management of canine laryngeal paralysis consists of symptomatic management of the upper airway obstruction and avoidance of stress, excitement, and increased environmental temperatures in affected dogs. Treatment of concurrent disease processes, such as hypothyroidism or myasthenia gravis, is helpful in some patients.

Definitive treatment of laryngeal paralysis is surgical. Numerous surgical techniques have been described, including ventriculocordectomy, partial arytenoidectomy, unilateral or bilateral arytenoid lateralization (laryngeal tie-back), and modified castellated laryngofissure.[6,8] Of these techniques, unilateral arytenoid lateralization has been associated with the lowest complication rates, shortest surgical time, and best overall survival time.[7,8] Postoperative complications are common and range from 10% to 58%.[8] The most commonly reported complication is aspiration pneumonia. Others include continued respiratory distress, megaesophagus, failure of surgical repair, unresolved coughing or gagging, persistent exercise intolerance, vomiting, seroma formation at the surgical site, and acute respiratory distress syndrome.[7,8]

Unlike dogs, cats do not commonly suffer upper airway disease resulting from laryngeal paralysis. Clinical signs of laryngeal paralysis in cats are consistent with disease of the upper airway and include voice change, coughing, tachypnea or dyspnea, stridor, dysphagia, weight loss, and anorexia. As with dogs, the etiology of laryngeal paralysis in cats is largely unknown, although congenital and acquired forms seem to occur.[12] Potential causes include neoplasia, neuromuscular disease, and complications post thyroidectomy.[12,13] Medical management of unilateral laryngeal paralysis in cats is often effective, and it has been suggested that surgical repair should be reserved for those with bilateral disease. Although postoperative complications also occur in feline patients, the reported complications differ from those of dogs and include failure of the surgical repair, coughing, and laryngeal stenosis.[12,13] In contrast to dogs, aspiration pneumonia has not been reported as a complication in cats.

16.6.2 Brachycephalic Syndrome

Brachycephalic syndrome is a term used to describe a combi-nation of primary and secondary anatomic abnormalities found in brachycephalic breeds that leads to varying degrees of upper airway dysfunction and obstruction. The primary abnormalities include stenotic nares, enlarged tonsils, and an elongated soft palate. In affected animals, increased resistance to airflow through the nasal passages requires that the animal create a high negative pressure to achieve adequate tidal volumes. This increase in negative pressure distal to the nasal passages causes the tissue to become hyperplastic. As the pressure increases, it can actually pull the soft tissue into the lumen and even cause collapse of these structures. Secondary abnormalities associated with brachycephalic airway syndrome result from the increase in negative pressure and include everted lateral saccules and laryngeal and tracheal collapse.[14] As affected patients become more excited and tachypneic, the increased resistance and airway obstruction leads to increased inflammation, swelling, and edema. These changes can further impair the animal's airway and cause more severe airway obstruction.

Diagnosis of brachycephalic syndrome is based on visual examination of the nares and evaluation of the oropharynx under light anesthesia. Cervical and thoracic radiographs will confirm a hypoplastic trachea. Virtually all anesthetic drugs relax the muscles of the upper respiratory tract. This is a concern in brachycephalic breeds because the negative pressure generated by the diaphragm, combined with the impaired muscle tone in the upper respiratory tract, can lead to further collapse of the upper airway.[14] The patient should be preoxygenated and anesthesia induction should be rapid to minimize the risks. (See Chapters 162 and 163, Sedation of the Critically Ill Patient and Anesthesia of the Critical Care Patient, respectively.)

The treatment for brachycephalic airway syndrome is surgical. Widening of the stenotic nares is thought to be the most important therapy because the other changes may occur secondary to the stenotic nares. For this reason, some authors have recommended widening the nares of affected dogs as young as 3 to 4 months,[15] and in a review of airway obstruction surgery in the dog, 96% of dogs improved after the procedure.[16] Other surgical therapies include soft palate resection, resection of everted laryngeal saccules, and removal of the tonsils. Recommended treatment of laryngeal collapse is a permanent tracheostomy. This is based on the high mortality associated with partial laryngectomies.[14,16]

Brachycephalic syndrome is a rare clinical condition in cats. It has been described in brachycephalic cats, such as Persians, but little is known about the clinical progression or therapy.[1]

16.6.3 Neoplasia

Primary laryngeal neoplasia is rare in dogs and cats.[17,18] Tumor types in dogs include chondroma, osteosarcoma, melanoma, mast cell tumor, oncocytoma, lipoma, carcinoma, myxochondroma, anaplastic fibrosarcoma, fibropapilloma, thyroid carcinoma, rhabdomyosarcoma, and squamous cell carcinoma.[17,18] In cats, the most common laryngeal tumor types include lymphosarcoma and squamous cell carcinoma, although adenocarcinoma has also been seen.[1,17,18] Diagnosis requires histopathology examination because benign lesions are radiographically and grossly indistinguishable. The treatment and prognosis for laryngeal neoplasia vary depending on the extent, tumor type, and metastasis. The prognosis generally is considered poor due to the difficulty of surgical resection.[18]

Primary tracheal tumors are an uncommon cause of upper airway disease in dogs and cats.[17,19,20] Numerous tumor types have been described in dogs, including adenocarcinoma, carcinoma, mast cell tumor, leiomyoma, extramedullary plasmacytoma, osteosarcoma, chondroma, chondrosarcoma, osteochondroma, and ecchondroma.[17,19] The most common tumor type reported in dogs is osteochondroma. In cats, tumor types include lymphosarcoma, adenocarcinoma, seromucinous carcinoma, adenoma, carcinoma, squamous cell carcinoma, histiocytic lymphosarcoma, and lymphoblastic lymphosarcoma, with lymphosarcoma and adenocarcinoma being the most common.[17,19,20]

Diagnosis of tracheal tumors is done using radiography. The air in the trachea outlines and provides contrast outlining the mass. Both cervical and thoracic radiographs should be taken because intratracheal masses can occur anywhere along the length of the trachea. Tracheoscopy is also useful and allows direct visualization of the mass, and provides the opportunity for biopsy or brush cytology. Treatment options for tracheal tumors include surgical removal, radiation therapy, and chemotherapy. The modality of choice will vary depending on the tumor type, extent, and location. The prognosis for tracheal tumors is extremely variable depending on the tumor type, extent of disease, and comorbid disease processes. Young dogs with osteochondromas have a positive prognosis, but due to the paucity of long-term follow-up in these cases, the overall prognosis remains guarded.

16.6.4 Inflammatory Laryngeal Disease and Granulomatous Laryngitis

Inflammatory laryngeal disease and granulomatous laryngitis are unusual causes of upper airway obstruction in cats. Clinical signs will vary depending on the severity of the inflammation and subsequent obstruction, although airway obstruction requiring an emergency tracheostomy has been reported.[21] The etiology of inflammatory and granulomatous laryngitis is unknown, but proposed underlying causes of inflammation include viral or bacterial infection, trauma from endotracheal intubation, a complication of laryngeal surgery such as vocal fold resection, and eosinophilic granuloma complex.[21-23] In all reported cases, radiographs of the larynx showed a soft tissue opacity or a narrowing of the lumen.[21-23] Gross examination of the larynx often reveals severe thickening or erythema of the larynx, and polypoid or nodular lesions have been reported (Color Plate 16-1).[21-23] The clinical, radiographic, and gross lesions of inflammatory or granulomatous laryngeal disease are indistinguishable from those of neoplasia, so histopathology is necessary to differentiate the two diseases. The prognosis for both is variable and there are few reported cases in the veterinary literature, but an excellent long-term response to surgery, antibiotics, or glucocorticoids has been reported.[21-24]

16.6.5 Nasopharyngeal Polyps

Nasopharyngeal polyps are a common cause of upper airway disease and obstruction in the cat. They originate from the mucosa that lines the middle ear, auditory tube, and nasopharynx. The underlying etiology in these cats is not known, although infectious, inflammatory, and congenital origins have been suggested.[1] Although polyps may be associated with infection, either bacterial or viral, a causal relationship has not been established. Diagnosis is made by radiographs and oropharyngeal examination.[25,26] Treatment consists of surgical resection, and this may be combined with a bulla osteotomy.[25,26] The most common complication is temporary Horner syndrome in cats that undergo a bulla osteotomy.[25] Prognosis for affected cats treated surgically is excellent.

16.6.6 Nasopharyngeal Infection or Abscess

Infection of the middle ear can lead to upper airway obstruction due to inflammation or an abscess in the auditory tube. This can occur secondary to bacterial infections, foreign body migration, fungal infection (usually cryptococcal rhinitis), or aberrant migration of *Cuterebra*. [1,27] Diagnosis is made by sutures and/or caudal rhinoscopy, but in cases of granuloma formation secondary to fungal infection or parasite migration, definitive diagnosis requires histopathologic analysis.[1,27] Treatment consists of surgical debulking and appropriate systemic antimicrobial or antifungal therapy.

16.6.7 Tracheal Collapse

Tracheal collapse is a common cause of upper airway disease in dogs. Toy breed dogs are predominantly affected, 70 and 71 Yorkshire terriers are the most commonly affected breed.[28,29] Classically the tracheal rings collapse on the dorsoventral aspect in combination with laxity of the dorsotracheal membrane.[28] The exact etiology of tracheal collapse is not known, but there are likely many contributing factors. These factors, such as hypocellular tracheal cartilage, denervation of the dorsal tracheal membrane, chronic lower airway disease, congenital malformations, extratracheal masses, trauma, or compression of the trachea secondary to cardiomegaly, can occur individually or in combination.[29]

Diagnosis of tracheal collapse is made using lateral thoracic radiographs taken during inspiration and expiration. When radiographs alone are not diagnostic, fluoroscopy may be helpful because of the dynamic nature of the collapse. Tracheobronchoscopy has also been recommended to confirm the diagnosis, grade the severity, and facilitate a bronchoalveolar lavage. At the time of anesthesia, a complete laryngeal examination should be performed to identify any edema, laryngeal collapse, or laryngeal dysfunction, because this has been associated with a worse outcome.[29] Samples obtained from bronchoalveolar lavage should be submitted for cytologic analysis, culture, and sensitivity testing. The most commonly isolated bacteria from dogs with tracheal collapse include *Pseudomonas, Staphylococci, Pasteurella,* and *Escherichia coli*. [28-30]

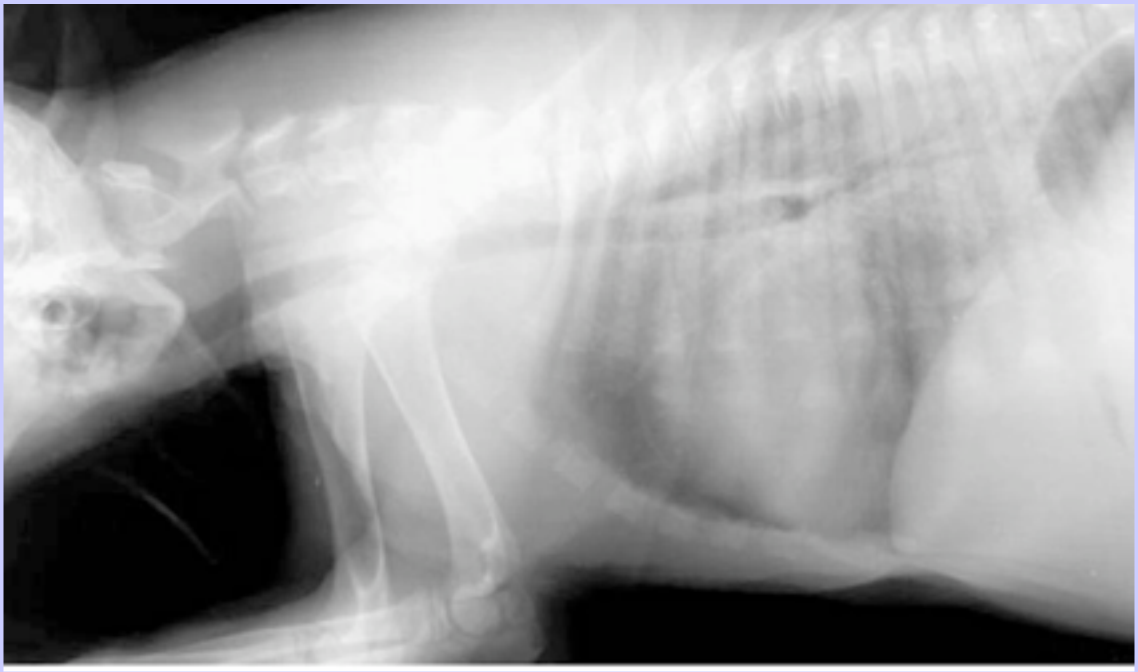
Treatment of tracheal collapse varies depending on the severity of the clinical signs, concurrent disease processes, and location and extent of the collapse. Medical treatment consists primarily of antitussive therapy and decreasing stressful stimuli. Other potential medical therapies include bronchodilators and intermittent steroid therapy. Overweight dogs should be put on a weight loss program, and a chest harness should be used instead of a neck lead. Patients should be treated for concurrent disease processes such as pneumonia or congestive heart failure.

In a study of 100 dogs with tracheal collapse, medical management provided long-term (greater than 12 months) resolution of clinical signs in 71% of patients.[31] When dogs fail to respond to medical treatment, surgical therapy is indicated. There are many surgical options, including tracheal ring chondrotomy, dorsal tracheal membrane plication, ventral placement of a synthetic tracheal ring prosthesis, tracheal resection and anastomosis, extraluminal polypropylene ring prosthesis, and intraluminal self-expanding wall stents.[28,29,31,32] For collapse affecting the thoracic trachea, extraluminal rings generally are not effective, and intraluminal self-expanding wall stents have been recommended (unless the mainstem bronchi also collapse). Complications from these implants include stent migration, granuloma formation, tracheal ulceration, tracheal necrosis, infection, and stent breakage. Commonly reported complications after surgery for tracheal collapse include coughing, continued dyspnea, and laryngeal paralysis secondary to damage to the recurrent laryngeal nerve. The overall prognosis for affected dogs is extremely variable and dependent on the severity, location, and extent of the collapse and comorbid disease processes.

16.6.8 Tracheal Stenosis

Tracheal stenosis is a rare cause of upper airway disease in dogs and cats. Clinical signs are consistent with upper airway disease, and the degree of respiratory distress will vary based on the extent and severity of the stenotic lesion. Causes include trauma, congenital malformation, aspiration of noxious substances, and tracheal injury secondary to endotracheal intubation.[33-36] Diagnosis is made with radiographs or tracheobronchoscopy. Surgical resection and anastomosis to remove the stenotic portion is recommended.

Figure 16-2 Noncardiogenic pulmonary edema in a dog. Note the alveolar disease located in the dorsocaudal lung fields.



16.7 SECONDARY COMPLICATIONS

Upper airway dysfunction and obstruction can lead to multiple, sometimes life-threatening sequelae. These complications include aspiration pneumonia (see Chapter 23, Aspiration Pneumonitis and Pneumonia), noncardiogenic pulmonary edema (Figure 16-2; see Chapter 21, Pulmonary Edema), and heat-induced illness (see Chapter 167, Heat Stroke). Radiographs often reveal a cranioventral interstitial to alveolar pattern in dogs affected with aspiration pneumonia. The radiographic pattern of noncardiogenic pulmonary edema is a mixed interstitial and alveolar pattern, primarily affecting the dorsocaudal lung fields (see Figure 16-2). The prognosis for patients affected by these complications is variable, depending on severity and comorbid disease processes. In a study of nine dogs with noncardiogenic pulmonary edema secondary to upper airway obstruction, the pulmonary edema resolved in all cases once the upper airway obstruction was treated.[36] No animal died from pulmonary edema.

16.8 SUGGESTED FURTHER READING*

DN Aron, DT Crowe: Upper airway obstruction: general principles and selected conditions in the dog and cat. *Vet Clin North Am Small Anim Pract*. **15**, 1985, 891, *A general review of the clinical and clinicopathologic changes associated with numerous causes of upper airway obstruction in the dog.*

KJ Drobatz, DK Macintire: Heat-induced illness in dogs: 42 cases (1976-1993). *J Am Vet Med Assoc*. **209**, 1996, 1894, *A retrospective study of heat-induced illness. Describes the historical, clinical, and clinicopathologic findings in affected dogs. Also discusses the clinical course and prognostic indicators.*

DE Holt: Upper airway obstruction, stertor, and stridor. In LG King (Ed.): *Textbook of respiratory disease in dogs and cats*. 2004, Elsevier, St Louis, *A thorough discussion of the clinical signs, physiology, and pathophysiology of upper airway obstruction. Diagnostic testing and initial management of affected patients are also covered.*

RM Jerram, TW Fossum: Tracheal collapse in dogs. *Compend Cont Educ*. **19**, 1997, 1049, *A review of the literature on tracheal collapse in dogs. Includes information on etiology and pathophysiology, diagnostic testing, medical treatment, surgical options, and complications. Provides a nice synopsis of all of the various studies evaluating surgical options.* 71

72 CM MacPhail, E Monnet: Outcome and postoperative complications in dogs undergoing surgical treatment of laryngeal paralysis: 140 cases (1985-1998). *J Am Vet Med Assoc*. **218**, 2001, 1949, *A retrospective study evaluating surgical techniques for treatment of laryngeal paralysis in dogs. Outcome, outcome factors, and postoperative complications are discussed.*

* See the CD-ROM for a complete list of references

17 Chapter 17 Endotracheal Intubation

Mack Fudge, DVM, MPVM, DACVECC

17.1 Key Points

- Careful airway assessment is an imperative first step in managing the critically ill and emergency patient.
- Prior planning and preparation are key and necessary steps to successful endotracheal intubation.
- Knowledge of and confidence in performing multiple techniques for airway access improve the odds for successful patient outcomes.
- Care must be taken to ensure effective patient oxygenation throughout the intubation process.

17.2 INTRODUCTION

Endotracheal intubation describes the procedure of inserting a tube into the trachea. The three main indications for tracheal intubation are: (1) provision of a patent airway in a patient with upper airway obstruction, (2) protection against aspiration in a patient without normal airway protection reflexes, and (3) administration of oxygen, gaseous anesthetics, or positive-pressure ventilation.[1-3] Intubation is a frequently performed and often lifesaving procedure in critically ill patients. Recognizing the need to intubate and understanding procedures to aid difficult intubation are essential skills for the critical care veterinarian.

17.3 AIRWAY ASSESSMENT

Airway assessment is the first priority in the evaluation of a critically ill or emergency patient. Both airway patency and protection must be ascertained. When upper airway disease is severe, rapid induction of anesthesia and tracheal intubation is indicated. If orotracheal intubation is unsuccessful, a temporary tracheostomy is required (see Chapter 18, Tracheostomy).

Any patient lacking an adequate gag reflex, as may occur with neurologic disease, sedative or anesthetic drug administration, or cardiopulmonary arrest, requires immediate intubation for airway protection, oxygen therapy, and positive-pressure ventilation as needed. The gag or swallow reflex can be assessed by inserting a tongue depressor into the pharynx.

17.4 ROUTINE INTUBATION

Intubation of animals with normal upper airway anatomy is commonly performed using laryngeal visualization and insertion of an appropriate sized, cuffed endotracheal tube. An adequate level of anesthesia is required. After correct placement is confirmed, the tube is secured by tying it around the maxilla or mandible, being sure that the tie lies caudal to both canine teeth. Alternatively, a tube can be tied around the back of the head. The tube usually is connected to an oxygen source such as a Bain circuit or an anesthetic machine circuit. Finally, the cuff is inflated until it gently occludes the airway exterior to the tube. To determine how much cuff inflation is required, a manual breath is delivered while simultaneously inflating the cuff and listening for resolution of the air leak around the endotracheal tube.[3]

17.4.1 Dogs

For routine intubation of the dog, a laryngoscope with a blade long enough to allow adequate visualization of the larynx is required. Intubation commonly is performed with the dog in sternal recumbency. An assistant holds the animal's upper jaw by grasping either side of the maxilla with one hand, keeping the head raised and extended. Either the assistant or the operator opens the mouth by pulling the tongue out and down, and the endotracheal tube is passed between the arytenoids.[3] Alternatively, many dogs can be intubated in lateral or dorsal recumbency without the aid of an assistant.

17.4.2 Cats

Routine intubation of cats is performed in a manner similar to that used for dogs, except application of lidocaine to the larynx is recommended before attempting intubation in an effort to prevent laryngospasm. Some operators favor the use of a stylet to stiffen the endotracheal tube for feline intubation.[3]

17.5 DIFFICULT INTUBATION

The possibility of a difficult intubation should be considered in animals with evidence of upper airway obstruction, trauma, or abnormal anatomy (e.g., brachycephalic breeds). Preplanning for intubation of cases such as these is essential to maximize the likelihood of success.

17.5.1 Preoxygenation

Any delay in intubation of a patient places the animal at risk of hypoxemia. When breathing room air, complete upper airway obstruction or apnea will lead to hypoxemia within approximately 3 minutes. Preoxygenation of a patient with 100% oxygen via a tight-fitting face mask can prevent hypoxemia for up to 10 minutes of airway obstruction or apnea. Although a study in human patients found preoxygenation not as effective as previously thought, it still is recommended before attempting intubation of any critically ill patient or any patient at risk of a difficult intubation or apnea.[4]

17.5.2 Equipment Setup

If a difficult intubation is anticipated, all equipment that may be required should be set up before the procedure. Endotracheal tubes of the size appropriate for the patient, in addition to several smaller sizes, should be selected. Stylets or a guide tube, such as a polyethylene urinary catheter, should also be available. Large-bore catheters for transtracheal gas insufflation and a surgical kit for an emergency tracheotomy in case intubation is unsuccessful should also be on hand.

17.5.3 Approach

Routine intubation should be attempted initially. Any fluid accumulation in the oropharynx should be removed by suction or with gauze swabs. If routine intubation is unsuccessful, intubation with a smaller size endotracheal tube may be possible. If an endotracheal tube cannot be passed, intubation with a guide tube is often possible. An endotracheal tube (routine size or smaller) with lubricant applied can then be passed over the stylet and introduced blindly into the trachea.[3] The stylet can then be removed.

17.6 ALTERNATIVE TECHNIQUES

17.6.1 Fiberoptic-Assisted Intubation

Fiberoptic-guided intubation via an oral route may be useful in some patients. The fiberoptic scope is introduced into the caudal oropharynx, permitting glottic visualization and endotracheal intubation. Various specialized fiberoptic laryngoscopes may be used for this technique.[1] Note that fiberoptic intubations, especially using the nasal route, may result in more severe pressor and tachycardiac responses than those observed with direct laryngoscopic intubations.[5]

17.6.2 Digital Palpation

In certain cases, digitally directed blind intubation may be a prudent and useful technique. Identifying key anatomic structures by palpation may facilitate a gentle insertion of the tip of the endotracheal tube into the airway. It is essential to always verify correct placement of the tube when using this technique.

17.6.3 Nasal Intubation

Intubation of a nasopharyngeal airway can be a useful adjunct in some patients. This technique is performed commonly in human patients in whom a larger nasal cavity may accommodate a tube large enough for a definitive airway. Nasal tubes used in veterinary patients usually do not permit an airtight seal of the trachea, but they do provide a good route for oxygen administration. This technique may be contraindicated in trauma patients with basilar skull fracture or disruption of the cribriform plate. In these cases, the airway tube may traverse the fractured cribriform plate and injure the brain.[1]

17.7 SURGICAL AIRWAY

In individual animals with prominent cricothyroid membranes, a cricothyroidotomy can be used to secure the airway for patients with severe facial trauma and for patients requiring an emergency tracheal intubation in which oral or nasal intubation was unsuccessful. Compared with a tracheotomy, cricothyroidotomy is probably less time consuming, easier to perform, associated with fewer complications, and more likely to result in a dependable airway. It may be later converted to a tracheostomy under more controlled conditions. Commercially available, prepackaged cricothyroidotomy kits may save time during resuscitation.[1] The potential problem with these kits is that they require the user to be familar with the contents, and equipment sizes may not be appropriate for a smaller veterinary patient.

17.8 OTHER OPTIONS

17.8.1 Retrograde Intubation

Retrograde intubation is another method for securing the airway in certain conditions. This technique requires retrograde placement of a guidewire or catheter via the cricothyroid membrane into the trachea and rostrally into the oropharynx. An endotracheal tube (or fiberoptic bronchoscope via the suction port, or a tube changer followed by an endotracheal tube) is then threaded over the guidewire and into the trachea.[1]

17.8.2 Transillumination

Transillumination of the soft tissues of the neck using a flexible lightwand device may be useful in select, especially light colored, patients. This may be a suitable technique for patients that are difficult to intubate but that are ventilating effectively and that have a trachea large enough to safely accommodate the lightwand. The lightwand is placed inside an endotracheal tube during intubation. As the tube is advanced through the glottic opening, a well-defined circumscribed glow is readily appreciated in the ventral neck just below the thyroid prominence. This light-guided technique may help to minimize cervical spine movement, especially useful in trauma, neurologic, or other patients with particularly difficult airways. It should be attempted only in animals with airways of sufficient size to accommodate the lightwand and still allow for some air movement around the wand.[1,6]

17.8.3 Cricoid Pressure

Cricoid pressure is a useful adjunct to tracheal intubation. Firm pressure, directed dorsally over the cricoid cartilage, collapses the esophagus and helps to prevent passively regurgitated gastric fluid from reaching the hypopharynx. This technique is used commonly in human patients with a high likelihood of vomition or regurgitation.[7]

17.9 NEEDLE CRICOTHYROIDOTOMY

If nasal or oral intubation is technically difficult and is not successful, an airway by another route or method may be indicated. Oxygen can be provided via a large-bore catheter inserted through the cricothyroid membrane or through the tracheal wall and attached directly to the gas outlet of an anesthesia machine. This technique is only a temporary adjunct that can buy time until a more permanent cricothyroidotomy or tracheotomy is performed. A high-frequency jet ventilator works well for this technique.[1] This percutaneous tracheotomy technique is a little quicker and easier to perform and may have less likelihood of postoperative infection than does a full tracheotomy.[8]

17.10 PLACEMENT VERIFICATION

Verification of correct placement of the endotracheal tube is a necessary and critical step. It is not uncommon, especially in hurried or difficult intubations, for the tube to be advanced inadvertently down the esophagus. The simplest and most obvious way to ensure correct placement is through direct visualization of the tube placement. Seeing the tube pass through the larynx and into the trachea should ensure correct placement. Measurement of exhaled carbon dioxide, either by a disposable colorimetric device or by an infrared carbon dioxide analyzer, can provide an additional level of assurance of correct tube placement. This technique is not recommended for intubations made during cardiac arrest. Other methods such as watching for fogging of the inside of the endotracheal tube during exhalation, vapor seen on shiny surfaces placed at the end of the tube, or fluttering of valves on connected anesthesia machines are often misleading and supportive at best.

17.11 COMPLICATIONS

Tracheal intubation can be associated with equipment-related or patient-related complications. Soft or particularly small endotracheal tubes can crimp because of the acute angle created as the tube passes from the oropharynx toward the larynx, reducing the airflow through the tube. This can lead to hypoventilation and subsequent hypercapnia and hypoxemia. Bending can also create additional pressure at the end of the tube that can damage the dorsal larynx or tracheal mucosa.

Pressure-induced tracheal necrosis is possible when the endotracheal tube cuff is over-inflated or the tube is too large for the patient. If the intubation is expected to be prolonged, take care to pad oral soft tissues that come into contact with the endotracheal tube. Prolonged contact of the tube with lips, gingiva, and tongue can cause multiple small areas of pressure necrosis. In rare cases of more extreme damage caused to the trachea by endotracheal tubes, subcutaneous emphysema or even pneumothorax are possible.

Endotracheal tubes may be unintentionally advanced too far and end in a mainstem bronchus, usually the right. This may lead to inadvertent overinflation of the intubated lung and impaired gas exchange. Premeasuring endotracheal tubes before placement and bilateral thoracic auscultation can help avoid inadvertant endobronchial intubation.

Endotracheal intubation can cause increased intracranial pressure and even increased intraocular pressure. It can also cause significant increases in blood pressure and heart rate.[9] Rapid, smooth intubation is important.

17.12 SUMMARY

Airway management is fundamental in the care of critically ill and emergency patients. Complications resulting from difficulties with airway management include brain injury, myocardial injury, increased intracranial and intraocular pressures, pulmonary aspiration of gastric contents, trauma to the airways, and death. Shock, respiratory distress, full stomach, airway trauma, cervical spine instability, and head injury may make emergency tracheal intubation a challenging procedure in the critically ill patient. Careful use of pharmacologic agents can greatly enhance the ability to safely secure the airway.

17.13 SUGGESTED FURTHER READING*

S Jaber, J Amraoui, JY Lefrant, et al.: Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Crit Care Med*. **34**, 2006, 2355, *A nice and current study in human patients looking at indications and complications associated with endotracheal intubation.*

FS Xue, CW Li, KP Liu, et al.: The circulatory responses to fiberoptic intubation: a comparison of oral and nasal routes. *Anesthesia*. **61**, 2006, 639, *A prospective clinical observation study looking at the hemodynamic effects of oral and nasal intubation using a fiberoptic device as an assist.*

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* See the CD-ROM for a complete list of references

18 Chapter 18 Tracheostomy

Mack Fudge, DVM, MPVM, DACVECC

18.1 KEY POINTS

- Continuous patient monitoring and intensive nursing care are critical to successful tracheostomy tube management and patient comfort.
- Care must be taken to prevent damage to the left recurrent laryngeal nerve when a tracheotomy is performed.
- Long stay sutures placed around the cartilage rings adjacent to the tracheotomy incision allow routine tube replacement and may be lifesaving if the tube becomes occluded or dislodged.

18.2 INTRODUCTION

Temporary tracheostomy is indicated for life-threatening upper airway obstruction, oral or pharyngeal surgery when oral endotracheal intubation is undesirable, airway obstruction from edema and inflammation after pharyngeal or laryngeal surgery, long-term ventilator support for critically ill patients, and removal of tracheal foreign bodies.[1] Access to the trachea provided by the tracheostomy allows air to enter distal to obstructions and reduces damage to the oral cavity from prolonged intubation.[2,3]

18.3 TRACHEOSTOMY TUBE SELECTION

Numerous tracheostomy tubes are commercially available. They can be cuffed or uncuffed tubes and may or may not have an inner cannula. The requirement for a tube cuff will depend on individual patient factors. In most cases a cuff is not required, and the use of an uncuffed tube or keeping the tube cuff deflated may reduce the likelihood of tracheal injury. A cuff may be considered desirable in patients that require positive-pressure ventilation, although this mode may also be feasible with uncuffed tubes. A tube cuff may make it necessary to use a slightly smaller tracheostomy tube than would be possible without the cuff.

A removable inner cannula allows for easy and effective tube maintenance and is considered desirable. The inner cannula can be removed briefly for cleaning without disrupting the airway integrity. Unfortunately, smaller tubes cannot be made with an inner cannula. In the absence of an inner cannula, the entire tracheostomy tube should be replaced every 24 hours (more often if indicated) to prevent occlusion with accumulated secretions.

The size of the tracheostomy tube chosen is based on the diameter of the patient's airway. The largest tube that can be readily accommodated by the trachea is selected. Note that the size of tracheostomy tube does not correspond with the scale used to size endotracheal tubes. An estimate of the appropriate tracheostomy tube size usually can be made by evaluation of the inner lumen diameter of the trachea on a lateral cervical radiograph.

Tracheostomy tubes can also be fenestrated. The fenestration is an opening in the tube that allows air flow through to the upper airway if the external opening is occluded. In human patients this feature is used to enable speech. The utility of a fenestrated tube in veterinary patients is questionable. A fenestrated tube cannot be used if positive-pressure ventilation is required.

If a tracheostomy tube is not immediately available, an endotracheal tube can be shortened and used effectively in the interim.

18.4 SURGICAL TECHNIQUE

Temporary tracheostomy is best performed in a controlled manner with the patient under general anesthesia with an orotracheal tube in place. The animal is placed in dorsal recumbency with the neck carefully extended for exposure of the surgical site. The neck can be elevated from the table by placing it on a cushion. Routine surgical preparation of the ventral cervical region is performed.

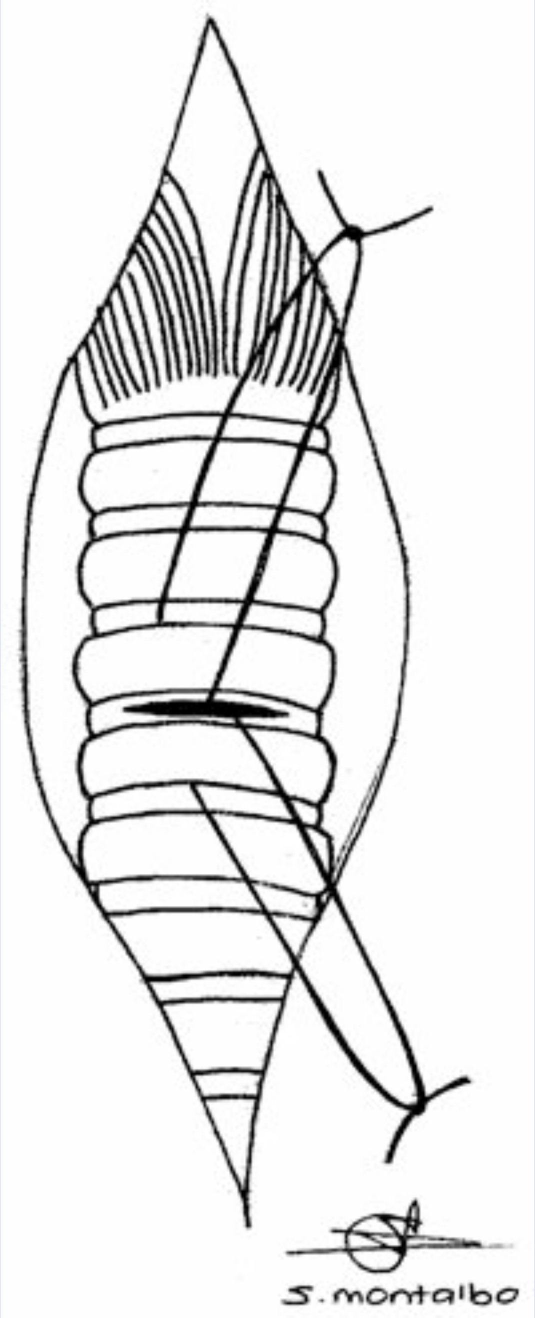
A 2- to 5-cm ventral cervical midline skin incision is made extending from the cricoid cartilage toward the sternum. The sternohyoid muscles are separated along their midline with blunt dissection and retracted laterally. The peritracheal connective tissue is removed from the region of the tracheotomy site. Throughout the procedure care must be taken to prevent dissection lateral to the trachea to prevent injury to the left recurrent laryngeal nerve or disruption of tracheal blood supply.

Various tracheal incisions have been proposed. Although most surgeons believe that a transverse approach is least likely to cause tracheal stenosis, studies suggest that the type of incision plays a minor role in the development of stenosis.[1,3-5] The two common surgical approaches for temporary tracheotomy are transverse and vertical incisions.

18.4.1 Transverse Incision

The annular ligament between the third and fourth or fourth and fifth tracheal rings is incised, taking care not to extend the incision longer than 50% of the tracheal circumference. Extreme care must be taken to avoid the left recurrent laryngeal nerve. A small ellipse of cartilage from each tracheal cartilage adjacent to the tracheotomy incision can be made to help reduce tracheal irritation and inflammation. Long loops of suture are placed around the tracheal rings adjacent to the incision to facilitate retraction of the trachea and future replacement of the tube after cleaning (Figure 18-1).[1,2]

Figure 18-1 Transverse incision tracheostomy.



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18.4.2 Vertical Incision

A ventral midline vertical incision is made through two to four tracheal rings. Long stay sutures may be placed encircling the cartilage rings lateral to the incision to aid in continued manipulation of the trachea and future tube replacement (Figure 18-2). Segmental lateral tracheal collapse may be a long-term complication of this procedure.[1,2]

Following tube placement via either technique the muscles and skin can be closed routinely, but space should be left around the tracheostomy tube so that air can escape easily to prevent subcutaneous emphysema.

18.4.3 Securing the Tracheostomy Tube

The tracheostomy tube can be secured with sutures or with umbilical tape tied around the neck. Commercially made Velcro-fastening tracheostomy tube ties are also available. The author prefers to tie the tube in place to facilitate regular tube replacement and reduce patient discomfort. Tube ties need to be evaluated frequently to prevent inadvertent tube dislodgement.

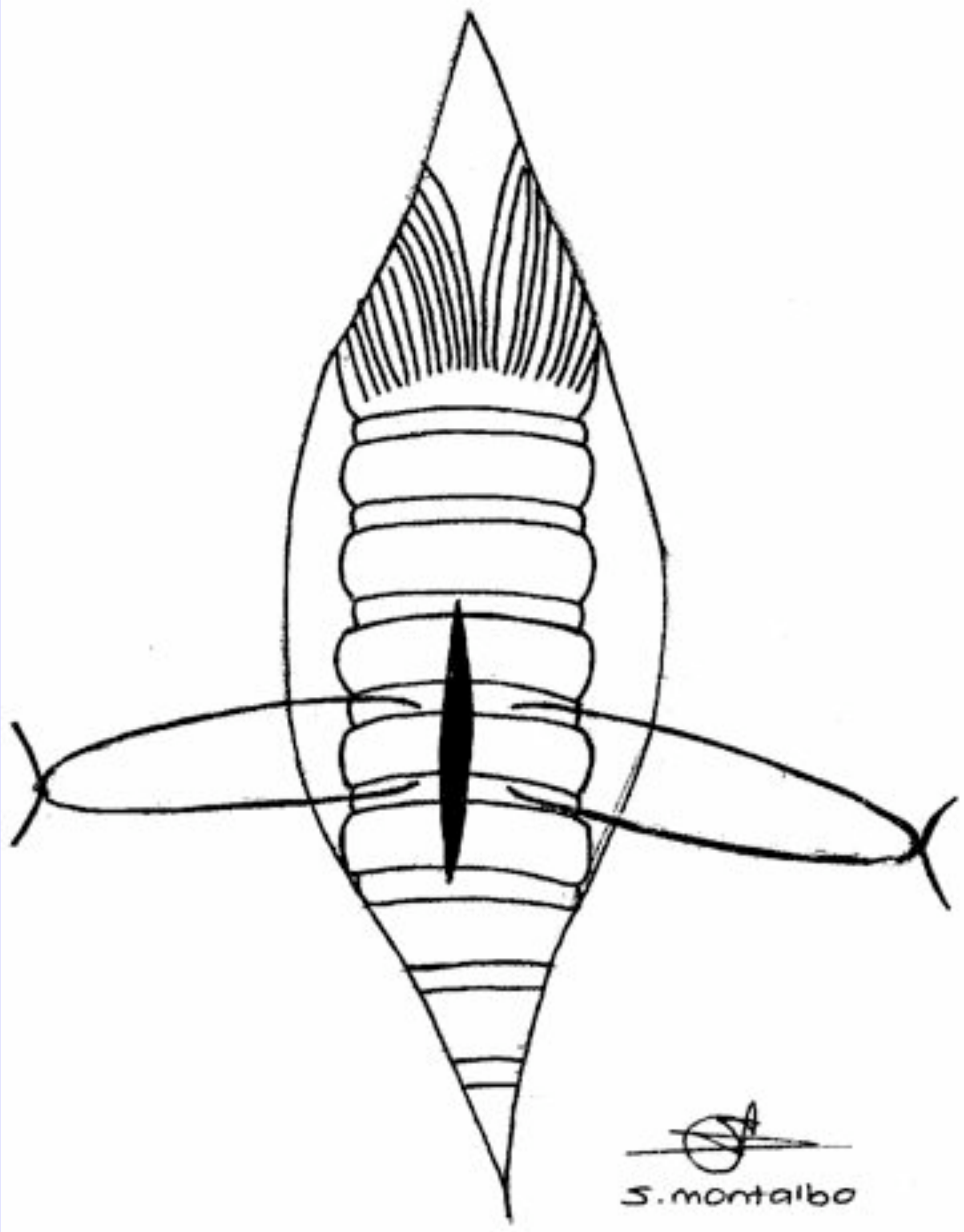
18.5 NEEDLE CRICOTHYROIDOTOMY

In cases of severe respiratory distress there may be insufficient time or inadequate preparation to perform a tracheostomy, and an airway by another route or method may be indicated. Using a needle cricothyroidotomy, oxygen can be provided via a large-gauge needle or catheter inserted through the cricothyroid membrane or through the tracheal wall. This technique is only a temporary adjunct used for minutes because ventilation will not be effective.[6] However, this technique can buy time until a better prepared, planned surgical procedure can be performed.

18.6 TRACHEOSTOMY TUBE MANAGEMENT

Tracheostomy tube management requires continuous intensive care monitoring.[1,3-5] When this level of care is unavailable, elective tracheostomy should not be done. When a tracheostomy is unavoidable, the patient should be transferred to a suitable facility for ongoing care as soon as possible.

Figure 18-2 Vertical incision tracheostomy.



The major aims of tracheostomy tube management are to prevent tube obstruction, to facilitate removal of airway secretions, and to minimize the risk of airway trauma or nosocomial pneumonia. It is important to recognize that tube occlusion or dislodgement can occur without warning despite ideal tube management, and staff should be prepared for rapid tube replacement (or inner cannula removal) should acute complications develop.[7,8] The placement of stay sutures around tracheal rings adjacent to the tracheotomy site at the time of surgery is essential to allow successful tube replacement. The author recommends that tape tabs be placed on the end of each stay suture and labeled *cranial* and *caudal* or *left* and *right* as appropriate. With the use of stay sutures most animals will tolerate tube replacement while awake, without sedation.

Patient positioning either in sternal recumbency with the neck extended or in dorsal recumbency with the neck extended is extremely important to facilitate this procedure. Gradual concretion of airway secretions within the lumen of the tracheostomy tube may occur despite regular suctioning. For this reason removal and cleaning of inner cannulas should be performed every 4 hours, and tubes without an inner cannula should be replaced every 24 hours routinely, even if there are no obvious problems.

18.6.1 Suctioning

Suctioning should be performed frequently to remove secretions from the airway and reduce the likelihood of tube occlusion. See Box 18-1 for a suggested protocol for tracheostomy tube management. Sterile technique should be used at all times. The suction catheter must be sterile as well as soft and flexible to minimize airway trauma. Human oxygen administration catheters work well for suctioning animal airways.

Sterile physiologic saline solution (1 to 2 ml) can be injected into the trachea through the tracheostomy tube to loosen exudates before suctioning. Respiratory distress or vagal stimulation (retching or vomiting) may occur during tracheal suctioning. The airway should be well humidified, and preoxygenation with 100% oxygen is recommended. The catheter is inserted down the airway, several centimeters beyond the length of the tube, and suction is applied as the catheter is withdrawn using a circular motion. The duration of suctioning should be brief (no more than 10 seconds) to minimize small airway collapse and 100% oxygen provided for at least 3 minutes immediately after each suctioning episode. Tracheostomy tube suctioning is performed routinely every 4 hours, although in some patients it may be necessary more frequently.

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18.7 TUBE REMOVAL

The tracheostomy tube is removed when an adequate upper airway is established. Most small animals that have a tracheostomy for upper airway surgery can be extubated within 48 hours after surgery. Once the tube has been removed, the tracheostomy site is left open and allowed to heal by granulation and epithelialization.

18.8 COMPLICATIONS

Complications following temporary tracheostomy include tube occlusion or dislodgement, subcutaneous emphysema, pneumothorax, aspiration of fluid or foreign bodies, and pneumonia. Arrhythmias and vagally mediated bradycardia and collapse can occur during suctioning or tube manipulation. With careful management and appropriate monitoring, most complications can be prevented.

18.8.1 Box 18-1 Tracheostomy Tube Care Protocol

- Remove inner cannula (if present) for cleaning and replace with the temporary cannula for the duration of the procedure.
- Airway humidification is recommended for 20 minutes before suctioning patients that are not on a mechanical ventilator.
- Preoxygenate with 100% oxygen for at least 3 minutes before suctioning.

- When suctioning, use sterile technique, insert the sterile catheter to the level of the carina, and apply suction as the catheter is removed with a circular motion (taking no longer than 10 seconds).
- Administer 100% oxygen for at least 3 minutes after each suctioning episode.
- Perform suctioning 2 to 4 times; frequency is guided by the amount of exudate and how well the patient tolerates the procedure.
- Replace cleaned inner cannula.
- Clean incision site surrounding tracheostomy tube and check that the tube is still secured appropriately.

18.9

SUGGESTED FURTHER READING*

MA Boucher, MA Edelman, KW Edmission, et al.: Tracheotomy. In EJ Mills (Ed.): *Handbook of medical-surgical nursing*. ed 4, 2006, Lippincott Williams & Wilkins, Ambler, PA, *A human nursing book that points out several nursing issues that can be incorporated thoughtfully into patient care and improve likelihood of therapeutic success in critically ill patients*.

RB Fingland: Surgical therapy and technique. In WW Campfield (Ed.): *Waltham symposium for the treatment of small animal diseases: emergency medicine and critical care*. 1991, Kal Kan Foods, Vernon, Calif, *An article from a collection of emergency and critical care topics compiled by Waltham; derived from a symposium conducted at Ohio State University; covers several surgical techniques commonly used in emergency situations*.

CS Hedlund: Surgery of the upper respiratory system. In TW Fossum (Ed.): *Small animal surgery*. 1997, Mosby, St Louis, *Chapter that provides nice descriptions and diagrams of many of the more common upper respiratory surgical procedures. Perhaps the best one-stop surgical reference book for practitioners*.

CS Hedlund: Surgical diseases of the trachea. *Vet Clin North Am Small Anim Pract*. **17**, 1987, 301, *An excellent review article describing tracheal surgery including tracheostomy*.

CS Hedlund: Tracheostomies in the management of canine and feline upper respiratory disease. *Vet Clin North Am Small Anim Pract*. **24**, 1994, 873, *A review article covering both permanent and temporary tracheostomy indications and perioperative problems*.

CS Hedlund: Tracheostomy. *Probl Vet Med*. **3**, 1991, 198, *A review of tracheostomies*.

I Scrase, M Woollard: Needle vs surgical cricothyroidotomy: a short cut to effective ventilation. *Anaesthesia*. **61**, 2006, 962, *A literature review covering various techniques for airway access in people via the cricothyroid route. Includes many sound principles that have merit in animal patients*.

RE St John, JF Malen: Contemporary issues in adult tracheostomy management. *Crit Care Nurs Clin North Am*. **16**, 2006, 413, *A nursing review of practice trends for managing tracheostomy tubes in human patients. Includes principles, equipment used, and their applications to patient care*.

* See the CD-ROM for a complete list of references.

19 Chapter 19 Oxygen Therapy

Elisa M. Mazzaferro, MS, DVM, PhD, DACVECC

19.1 KEY POINTS

- Hypoxemia occurs in a variety of critical illnesses. Oxygen supplementation can improve oxygen delivery and decrease the incidence of lactic acidosis.
- Supplemental oxygen administration should be provided whenever a patient's partial pressure of arterial oxygen (PaO_2) is less than 70 mm Hg, oxygen saturation (SaO_2) is less than 93% on room air, and in cases of significant anemia or cardiovascular instability.
- Noninvasive means of oxygen supplementation, including flow-by, mask, hood, and oxygen cage, are a simple means of providing an oxygen-enriched environment to a critically ill patient.
- Nasal and nasopharyngeal oxygen supplementation require minimal equipment and are well tolerated by many hypoxemic patients.
- Tracheal oxygen supplementation provides a higher fraction of inspired oxygen (FiO_2) than nasal or noninvasive means of oxygen therapy, but it is technically more difficult and has higher inherent risks to the patient.

19.2 INTRODUCTION AND INDICATIONS FOR OXYGEN THERAPY

Hypoxemia is defined as a deficiency of oxygen in the arterial blood.[1,2] Hypoxemia can occur as a result of hypoventilation, ventilation-perfusion mismatch, diffusion impairment, decreased oxygen content of inspired air, and intrapulmonary or cardiac shunting. Global hypoxemia can occur in a variety of critical illnesses, including pulmonary parenchymal, neuromuscular, pleural cavity, chest wall, and cardiac disease. Hypoxemia results in inadequate delivery of oxygen to the tissues and subsequent cellular hypoxia. Systemic illnesses such as sepsis, systemic inflammatory response syndrome (SIRS), anemia, and acid-base imbalances such as a metabolic or respiratory alkalosis or acidosis can also contribute to inadequate tissue oxygen delivery.

Oxygen supplementation is one of the most important management tools for a variety of critical conditions, including cardiopulmonary disease, sepsis, SIRS, and head trauma. Delivery of oxygen to tissues is affected by the patient's arterial oxygen content (CaO_2) and cardiac output (Q). The formula to calculate arterial oxygen content is as follows:

$$\begin{aligned} CaO_2 = {} & [1.34(\text{ml } O_2 / \text{g}) \times SaO_2(\%) \times \text{hemoglobin}(\text{g}/\text{dl})] \\ & +[PaO_2(\text{mm Hg}) \times 0.003(\text{ml } O_2 / \text{dl} / \text{mm Hg})] \end{aligned}$$

where (SaO_2) is arterial oxygen saturation and (PaO_2) is partial pressure of arterial oxygen.

Arterial oxygen content depends on the concentration of hemoglobin as well as the binding affinity and the SaO_2 of the hemoglobin. Most of the arterial oxygen is carried to tissues while bound to hemoglobin. A small fraction is carried dissolved (or unbound [$0.003 \times PaO_2$]) in plasma and subsequently diffuses into the tissues. Providing supplemental oxygen to increase the fractional concentration of oxygen in inspired gas (FiO_2) above 21% is an effective means of increasing both bound and unbound oxygen in arterial blood, provided that a cardiac or pulmonary parenchymal shunt is not present.[1]

Supplemental oxygen should be provided whenever a patient's PaO_2 is less than 70 mm Hg or SaO_2 is less than 93% on room air.[1] Oxygen administration can be divided into noninvasive and invasive techniques. The method of supplementation is dependent on each patient's needs and tolerance, patient size, degree of hypoxemia, desired FiO_2, anticipated duration, clinical experience and skill, and the equipment and monitoring means available.[2]

19.3 HUMIDIFICATION

Oxygen supplementation can be accomplished in a number of ways. All methods require some kind of humidification if used for more than several hours. Otherwise the patient is likely to experience drying and dehydration of the nasal mucosa, respiratory epithelial degeneration, impaired mucociliary clearance, and an increased risk of infection.[2] A supplemental oxygen source can be humidified easily by bubbling the oxygen through a tube that is submerged in a bottle of sterile saline.[2] The humidified oxygen then accumulates above the surface of the solution. The gas that collects can then be delivered through a length of tubing to the patient's oxygen delivery device, whether it is a mask or tube into some component of the respiratory tract.

19.4 NONINVASIVE METHODS OF OXYGEN SUPPLEMENTATION

19.4.1 Flow-By Oxygen

Flow-by oxygen supplementation is one of the simplest techniques to use in an emergency setting. A length of oxygen tubing connected to an oxygen source is held adjacent to or within 2 cm of a patient's nostril or mouth. An oxygen flow rate of 2 to 3 L/min generally provides an FiO_2 of 25% to 40%.[3] This technique is well tolerated by most patients and can be used during the initial triage and patient assessment. Because this technique also delivers a large quantity of oxygen to the surrounding environment, it is wasteful and not appropriate or economical for long-term use.

19.4.2 Face Mask

Short-term oxygen supplementation can be accomplished by placing a face mask over a patient's muzzle, then delivering oxygen (humidified if oxygen administration of more than a few hours is required) or tank oxygen in a circle rebreathing or a nonrebreathing circuit. With a tight-fitting face mask, flow rates of 8 to 12 L/min can provide an FiO_2 of up to 50% to 60%.[3] With loose-fitting face masks, higher flow rates of 2 to 5 L/min are recommended, depending on the size of the patient and degree of hypoxemia. With a tight-fitting face mask, rebreathing of carbon dioxide can occur, as well as dangerous increases in temperature and humidity. The face mask should be vented periodically, or changed to a looser face mask or other means of oxygen supplementation as soon as possible.

Awake and coherent patients may not tolerate oxygen delivered by face mask for long periods. An attendant must be present to ensure that the mask does not become detached and that the patient does not struggle or damage its eyes with the edge of the mask.[4] Advantages of this technique are that minimal equipment is required and that the patient can be simultaneously treated and evaluated in emergency situations.

19.4.3 Oxygen Hood

Several varieties of oxygen hood are available from commercial manufacturers, or they can be made easily in the hospital with clear plastic wrap such as Saran Wrap, tape, and a rigid Elizabethan collar (or recycled x-ray film of appropriate size). To create an oxygen hood, the front of a rigid Elizabethan collar is covered with lengths of clear plastic wrap taped in place. A small portion of the front is left open to room air to allow the hood to vent. The collar is then placed around the patient's neck and secured snugly. A length of oxygen tubing is inserted through the back of the collar and taped to the inside of the collar so that it will not be dislodged with patient movement. Once the hood has been flooded with oxygen (1 to 2 L/min), flow rates of 0.5 to 1 L/min typically will deliver an FiO_2 of 30% to 40%,[5] depending on the size of the patient and how tightly the collar fits. With extremely small patients, such as toy breeds or neonates, the entire patient can be placed in the collar for a homemade oxygen tent or minicage. Some patients will not tolerate the collar and can become hyperthermic. If the hood is left unvented, carbon dioxide and moisture can accumulate within the hood and contribute to patient distress. Overall, an oxygen hood is an economical and practical means of supplemental oxygen administration and is well tolerated by most patients.

19.4.4 Oxygen Cage

Supplemental oxygen can be delivered into a Plexiglas box to administer higher FiO_2 concentrations than are possible with nasal, hood, or flow-by methods.[4] Oxygen cages that control oxygen concentration, humidity, and temperature are available from commercial sources. The cages are vented to decrease buildup of expired carbon dioxide. Oxygen cages can be made from human pediatric incubator units into which humidified oxygen is supplied through a length of tubing. The FiO_2 can reach up to 60%, depending on the size of cage and patient and oxygen flow rate, but it typically is maintained at 40% to 50%.[2,4] Oxygen cages are very useful, but they are an expensive means, because oxygen is released from within the cage into the external environment whenever the cage is opened. In some patients, hyperthermia can develop if the temperature within the cage is not monitored and maintained at 70° F (22° C).[4] Ice packs can be placed in an oxygen cage to decrease ambient temperature, but they should not be placed in contact with the patient because peripheral vasoconstriction can exacerbate hyperthermia.

Although many authors describe lack of direct patient access as a disadvantage of this technique, continuous observation and continuous assessment of pulse oximetry, blood pressure, and ECG allow patient monitoring through the Plexiglas cage doors.[4] Precaution must be taken when placing animals with upper airway obstruction in the oxygen cage, because the observer's ability to hear stertor or stridor through the cage door is diminished.

19.5 INVASIVE METHODS OF OXYGEN SUPPLEMENTATION

19.5.1 Nasal and Nasopharyngeal Oxygen

If supplemental oxygen will be required for more than 24 hours and an oxygen cage is not readily available or feasible, a nasal or nasopharyngeal oxygen catheter should be considered in dogs. Nasal oxygen catheters are fairly simple to place, require minimal equipment, and are well tolerated by most patients.[6] Oxygen insufflation catheters can be placed in the nasal cavity or directly into the nasopharyngeal region by a similar technique.

To place a nasal oxygen catheter, the patient's nasal passage should be anesthetized first with topical 2% lidocaine or proparacaine. Next, a 5 to 10 Fr red rubber or polypropylene catheter should be held along the side of the nose, the tip placed at the lateral canthus of the eye, and a mark made on the tube with a permanent marker at the nostril level (Color Plate 19-1). The tip of the tube is lubricated and the tube gently inserted into the ventral nasal meatus to the level of the mark on the tube. The tube can be secured adjacent to the nostril with suture or staples. The external tubing can then be secured to the lateral maxilla or between the patient's eyes with suture or staples. To help prevent patient intolerance of the tube, be sure to avoid securing the tube to the patient's whiskers.

Oxygen should be provided from a humidified source to avoid drying and irritation of the nasal mucosa. Nasal catheters can provide a wide range of FiO_2, depending on the size of the animal, respiratory rate, and panting or mouth breathing.[4,7] Flow rates of 50 to 150 ml/kg/min can provide 30% to 70% FiO_2.[2,8,9] Higher flow rates can be irritating to the patient and cause sneezing. Sneezing and patient intolerance can be alleviated in most cases by reapplying the topical anesthetic or advancing the nasal catheter into the nasopharyngeal region.

Nasopharyngeal catheter placement is almost identical, inserting it into the nasal meatus, with the exception of the anatomic landmark for measuring the tube. After the topical anesthetic has been applied, the catheter is held along the side of the face with the tip placed at the ramus of the mandible; the catheter is marked at the level of the nostril. The lubricated tube is then inserted ventromedially into the nasal meatus. To facilitate passage of the tube ventrally and medially to the turbinates, the lateral aspect of the nostril should be pushed medially, and the patient's nasal philtrum pushed dorsally, as the tube is passed. Once the tube has been passed to the level of the mark, it can be secured to the patient's face in a manner identical to that used with the nasal oxygen catheter. Overzealous pressure as either tube is placed can cause epistaxis.

Following insertion of a nasal or nasopharyngeal catheter, an Elizabethan collar should be placed to help prevent 79
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tube dislodgement by the patient. A length of oxygen tubing can be attached to the proximal end of the tube with a cut 1-ml syringe or Christmas tree adapter and then attached to a humidified oxygen source. Alternatively, nasal prongs can be placed in the nares of larger animals. These are very simple to use and well tolerated by dogs but require close observation because they can easily be dislodged by the patient.

19.5.2 Transtracheal Oxygen

Tracheal catheter placement is an effective means of administering supplemental oxygen to patients that are intolerant of nasal or hood oxygen or are panting or open-mouth breathing or have an upper airway obstruction. Although this technique is more labor intensive and requires a higher degree of skill than placement of a nasal catheter, higher FiO_2 with a degree of continuous airway pressure is provided[10] and can be beneficial for patients that require a higher degree of supplemental oxygen than that provided with a nasal catheter, but that do not require assisted ventilation.

Two methods of transtracheal oxygen supplementation have been described. The first method utilizes a through-the-needle large-bore catheter placed percutaneously through the skin and underlying tissues directly into the trachea.[4] The patient's ventrocervical region should be clipped from just caudal to the larynx to the thoracic inlet and laterally off of midline. To avoid iatrogenic introduction of bacteria and debris into the tracheal lumen, aseptic technique must be followed at all times. The clipped area should be aseptically scrubbed. A small bleb of

2% lidocaine should be placed at the level of the third to fifth tracheal ring, infiltrating the subcutaneous tissues and skin as the needle is backed out. The area is aseptically scrubbed again.

Wearing sterile gloves, the operator gently palpates and then grasps the patient's trachea with the fingers for stabilization. A small nick incision can be made through the skin with a No. 11 scalpel blade to decrease tissue drag as the catheter is inserted. The needle of the catheter is then inserted through the skin, through the subcutaneous tissue and sternohyoideus muscle, between tracheal rings, and into the trachea. A pop will be felt as the needle enters the trachea. Once in place, the catheter with stylette is inserted through the needle into the tracheal lumen. The needle is then removed from the trachea once the catheter has been inserted to its hub. Depending on the size of the animal, the distal end of the catheter may reach the carina.

The catheter can be connected to a humidified oxygen source with a cut 1-ml syringe and oxygen run at a flow rate of 50 to 150 ml/kg/min.[10] The catheter should be secured to the neck with lengths of white tape. Caution must be exercised to monitor the patient carefully, because ventral flexion of the neck or excessive skin folds can cause catheter kinking and occlusion. Excessive skin folds can be pulled dorsally and secured on the dorsal cervical midline with several horizontal mattress sutures until the catheter is no longer required.

The second method of transtracheal oxygen supplementation is more invasive and requires heavy sedation or a short-acting anesthetic agent. The choice of sedative/anesthetic drug should be made in light of the patient's clinical state. The ventrocervical region should be clipped and aseptically scrubbed in a manner identical to that described previously. The area should be aseptically draped with sterile towels and infiltrated with a local anesthetic (2% lidocaine 1 to 2 mg/kg). A midline skin incision should be made over the third to fifth tracheal rings. The subcutaneous tissues and sternohyoid muscle should be bluntly dissected with a curved hemostat or tips of a Metzenbaum scissors until the trachea is visible.

A small incision is then made between the fourth and fifth tracheal rings with a No. 11 scalpel blade, taking care to avoid cutting more than 50% of the circumference of the trachea. A curved hemostat is used to open the hole between tracheal rings, and a grooved director (from a spay pack) inserted into the tracheal lumen. A large-bore fenestrated catheter with a styletlte (Global Product) is then inserted into the tracheal lumen along the grooved director (Color Plate 19-2). Once the catheter is inserted, the grooved director and catheter stylet can be removed and the catheter secured. A sterile 4 × 4 gauze square with antimicrobial ointment should be placed over the incision and the catheter secured with lengths of white tape.

The cranial and caudal edges of large skin incisions should be sutured with nonabsorbable suture. The benefits of this technique are that larger catheters can be inserted and continuous airway pressure can be administered at higher oxygen flow rates than is possible with other methods of supplementation. Oxygen flow rates of 50 ml/kg/min are required to achieve 40% to 60% FiO_2.[10] This technique is well tolerated by many patients and is economical, but has the inherent risks associated with sedation, general anesthesia, and introduction of bacteria directly into the tracheal lumen. Jet lesions and damage to the trachea can occur with this technique.[4]

19.6 HYPERBARIC OXYGEN

A hyperbaric chamber provides 100% oxygen under supraatmospheric pressures (>760 mm Hg) to increase the percentage of dissolved oxygen in the patient's bloodstream by 10% to 20%.[1,9,11] Dissolved oxygen can diffuse readily into tissues that are damaged and may not have adequate circulation. Hyperbaric oxygen has been recommended for the treatment of severe soft tissue lesions including burns, shearing injuries, infection, and osteomyelitis. Ruptured tympanum and pneumothorax have been associated with hyperbaric oxygen therapy.

Hyperbaric oxygen is rarely used in veterinary medicine, given the expense of the equipment and space required for a specialized "dive chamber" in which to place the patient during treatment. An additional disadvantage is that once the dive chamber has been pressurized to supraatmospheric levels, it cannot be opened to gain patient access should complications occur.

19.7 COMPLICATIONS OF OXYGEN THERAPY AND OXYGEN TOXICITY

Supplemental oxygen is not an innocuous therapy. Hypercapnia is the primary stimulus for respiration in normal patients. In patients with chronic respiratory disease and hypercapnia, however, hypercapnic respiratory drive is diminished or lost, and the patient becomes largely dependent on hypoxemia as a respiratory stimulant. The administration of supplemental oxygen to a chronically hypercapnic patient depresses the hypoxic respiratory drive and can result in severe hypoventilation and respiratory failure. Mechanical ventilation may be necessary to treat the severe hypercapnia and hypoxemia that develop.[1]

Oxygen can be directly toxic to the pulmonary epithelium. The severity and timing of injury are dependent on the FiO_2 and duration of therapy. Pulmonary oxygen toxicity can be divided into five distinct phases. During the *initiation* phase, oxygen-derived free radical species such as superoxide anion, peroxide, and hydroxyl radicals cause direct damage to pulmonary epithelial cells as cellular antioxidant stores become depleted.[1,9] The initiation phase occurs within 24 to 72 hours of exposure to 100% oxygen.[1] Next, destruction of the pulmonary epithelial lining causes airway inflammation and the recruitment of activated inflammatory cells to the site. During this *inflammatory* phase, massive release of inflammatory mediators results in increased tissue permeability, and pulmonary edema develops. Severe local destruction occurs and is associated with high patient mortality rates. If the patient survives the *destruction* phase, type II pneumocytes and monocytes increase during a stage of *proliferation*. Finally, collagen deposition and interstitial fibrosis occur and can result in permanent damage to the lungs. An FiO_2 of over 60% should not be administered for longer than 24 to 72 hours, to avoid pulmonary oxygen toxicity.[9] Fortunately, without mechanical ventilation or an oxygen cage, an FiO_2 greater than 60% is difficult to obtain, making the risk of pulmonary oxygen toxicity minimal with most methods of oxygen supplementation.

19.8 SUGGESTED FURTHER READING*

MA Camps-Palau, SL Marks, JL Cornick: Small animal oxygen therapy. *Comp Cont Educ Pract Vet*. **21**, 2000, 587, *This is a good review article that describes hypoxemia and methods of oxygen supplementation*.

KJ Drobatz, S Hackner, S Powell: Oxygen supplementation. In JD Bonagura (Ed.): *Kirk's current veterinary therapy*. ed 13, 2000, Saunders, Philadelphia, *This is a good review of methods of oxygen supplementation*.

SL Marks: Nasal oxygen insufflation. *J Am Anim Hosp Assoc*. **35**, 1999, 366, *This is a short clinical pearl that describes indications for and placement of catheters for nasal oxygen insufflation*.

LW Tseng, KJ Drobatz: Oxygen supplementation and humidification. In LG King (Ed.): *Textbook of respiratory disease in dogs and cats*. 2004, Elsevier, St Louis, *This chapter describes pathophysiology and consequences of hypoxemia and methods of supplemental oxygen administration to small animal patients*.

* See the CD-ROM for a complete list of references

20 Chapter 20 Allergic Airway Disease In Dogs And Cats And Feline Bronchopulmonary Disease

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20.1 KEY POINTS

- Allergic airway disease in dogs and cats encompasses a broad spectrum of diseases that are somewhat poorly defined, but the clinical signs and pathologic appearances are similar for all causes.
- Diseases commonly included in this category include parasitic allergic airway disease, allergic bronchitis (eosinophilic bronchopneumopathy), feline asthma, and pulmonary infiltrates with eosinophils.
- Lower airway inflammation in response to either an extrinsic noxious stimuli or intrinsic hypersensitivity to antigenic stimulation is a known factor in the development of allergic respiratory disease in small animals. The airway inflammation causes mucosal edema, airway smooth muscle hypertrophy and constriction, and excessive production of airway secretions.
- Although the causes of both canine and feline allergic airway disease are numerous, the medical management is similar because it is often difficult to remove the inciting cause (unless infectious in nature). The clinician must therefore attempt to control and dampen symptoms.
- Steroids, bronchodilators, and oxygen therapy are the mainstays of emergency therapy for animals with allergic airway disease.

20.2 Definition of Allergic Airway Disease

Allergic airway disease in dogs and cats encompasses a broad spectrum of diseases that are somewhat poorly defined, but the clinical signs and pathologic appearances are similar regardless of causes. Diseases commonly included in this category are parasitic allergic airway disease, allergic bronchitis (eosinophilic bronchopneumopathy), feline asthma, and pulmonary infiltrates with eosinophils (PIEs). These diseases typically are characterized by bronchial or alveolar inflammatory changes including submucosal wall edema, increased bronchial secretions, smooth muscle hypertrophy, and smooth muscle constriction of the bronchioles and small bronchi. Histologically, there is typically a predominance of eosinophils within the airways and submucosa of the bronchial tree. Clinical signs include labored breathing, rapid shallow breathing, increased expiratory effort, and cough. Studies have shown variable degrees of inherent hypersensitivity in the bronchiolar smooth muscle in small animals with lower airway disease.[1,2] Animals may have an acute onset of respiratory signs with completely reversible changes or may develop chronic disease (defined as more than 2 months duration) that is associated with irreversible bronchial wall alterations.[3] The pathogenesis of these diseases has not been as thoroughly investigated as has human asthma. One should avoid terming small animal allergic airway disease as *asthma* because the pathogenesis and definition are much less clear than they are in humans.[4]

20.3 HUMAN ASTHMA

Human asthma is defined as a disease of the lower airways that makes affected individuals prone to inappropriate airway narrowing in response to a wide variety of provoking stimuli. The ease with which these airways narrow is termed *hyperreactivity*. [5] Human asthmatic patients will develop large numbers of immunoglobulin E (IgE) antibodies in response to various inhaled allergens. These IgE antibodies then crosslink to mast cells in the submucosa of the bronchi and bronchioles of the lung, causing mast cell degranulation. Degranulation leads to the release of several inflammatory mediators (i.e., histamine, leukotrienes, eosinophilic chemotactic factor, bradykinin) that cause immediate airway constriction, as well as a late-phase inflammatory response that takes place several hours after initial release secondary to the effects of the leukotrienes.[5–7] These mediators are responsible for pulmonary mucosal edema, smooth muscle hypertrophy of the bronchi and bronchioles, accumulation of pulmonary secretions, and airway narrowing.[6] Because expiratory resistance and function is the primary breathing phase affected, there is air trapping within the lungs that leads to an increase in functional residual capacity (FRC) and appears radiographically as hyperinflation of the lungs.[6,8]

20.4 PATHOGENESIS OF SMALL ANIMAL ALLERGIC RESPIRATORY DISEASE

The pathophysiology of small animal allergic airway disease is less well understood than human asthma, but it is clear that these diseases in small animals are characterized clinically by a cough, typically a prominent increase in expiratory effort with or without appreciable wheezes, and a predictable response to glucocorticoids.[2,4,9] Allergic airway disease in small animals commonly causes an increase in the numbers of eosinophils within the airways, hyperinflation of the lungs, and thickening of the bronchi and bronchioles. Lower airway inflammation, in response to either an extrinsic noxious stimulus or intrinsic hypersensitivity to antigenic stimulation, is a known component in animals with allergic respiratory disease. The airway inflammation causes mucosal edema, airway smooth muscle hypertrophy and constriction, and excessive production of airway secretions.[3,9] Although similar in clinical picture and treatment, diseases such as feline and canine bronchitis should not be termed *allergic* in nature because they do not fit all of the above criteria (particularly overabundance of eosinophils in the airways). Diseases that should be included in small animal allergic airway disease include canine allergic bronchitis (also termed *eosinophilic bronchopneumopathy*), parasitic larval migration, PIE, and feline asthma.[10] Although the clinical picture and treatment of feline bronchopulmonary disease and feline asthma are similar, it is important to remember that they may have separate causes, because the cytopathologic features differ.

20.5 PARASITIC ALLERGIC AIRWAY DISEASE

Intestinal parasite migration as well as primary pulmonary parasitism can cause a parenchymal or lower airway allergic inflammatory response. The most common migratory parasite to cause an allergic response in the canine lungs is *Toxocara canis*. An inflammatory "allergic" reaction can take place in the lower airways and parenchyma of young dogs when this parasite migrates through the lungs as part of its normal development. Because of antigenic stimulation and the eosinophilic infiltrate induced by the larvae, these dogs may develop signs of respiratory disease that can vary in intensity.[11]

Other, less common parasites known to migrate through the lungs include *Ancylostoma caninum* (dogs only) and *Strongyloides stercoralis* (dogs or cats). Primary lung parasites include *Paragonimus kellicotti, Aelurostrongylus abstrusus, Capillaria aerophila,* and *Filaroides hirthi* (Table 20-1). *Dirofilaria immitis* (heartworm infection) can also cause an allergic inflammatory response when large numbers of antimicrofilarial antibodies entrap microfilariae within the pulmonary capillaries.[12] All of these parasites elicit predominantly a type I hypersensitivity reaction in the lungs that leads to bronchoconstriction and inflammation within the airways and lung parenchyma.[11]

Clinical signs associated with larval migration or primary pulmonary parasitic infection vary markedly from asymptomatic to severe coughing, wheezing, and respiratory distress. A complete blood count may show eosinophilia or basophilia, however this finding is not always present in animals suffering from parasitic allergic airway disease. Chest radiographs can show a variety of changes, including interstitial infiltrates, bronchial thickening, and even alveolar consolidation. *Ancylostoma caninum* and *Toxocara canis* can be seen using routine fecal flotation techniques. [10] *Strongyloides stercoralis* is more reliably found with the Baermann technique. However, negative fecal examination results do not rule out the possibility of migrating larval airway disease. Ova are often difficult to find on fecal examination because larvae typically begin to migrate through the lungs before shedding ova into the intestinal tract.[13]

Initially, a course of an appropriate antihelminthic medication (ivermectin or fenbendazole) can be used for treatment, particularly in mild to moderate clinical cases (see Table 20-1). Appropriate treatment for infection with *D. immitis* is discussed elsewhere.[14] In situations in which the clinical signs are severe, or fail to resolve completely, an antiinflammatory dosage of prednisone (0.5 to 1 mg/kg q24h) may be used to help control the disease manifestations.[10,11]

20.6 CANINE ALLERGIC BRONCHITIS OR EOSINOPHILIC BRONCHOPNEUMOPATHY

Canine allergic bronchitis (eosinophilic bronchopneumopathy) is characterized by pulmonary hypersensitivity with eosinophilic infiltration of lung and bronchial mucosa. The signalment of dogs with this disease tends to be different from that of either PIE or canine chronic bronchitis; these dogs tend to be younger (mean ± SD = 3.3 ± 2 years) and Siberian Huskies and Alaskan Malamutes are overrepresented. These dogs usually are in good physical condition, but show clinical signs such as coughing, labored breathing, or nasal discharge that is mucopurulent or yellow-green in appearance.[12,15]

Table 20-1 Parasitic Diseases That May Cause an Inflammatory Pulmonary Reaction*

Parasite	Species	Location	Diagnosis	Management
Aelurostrongylus abstrusus	Cats	Southern United States and worldwide	Larvae in tracheal wash or fecal Baermann technique	Fenbendazole or ivermectin if clinical
Capillaria aerophila	Dogs and cats	Worldwide	Eggs in tracheal wash or fecal flotation	Fenbendazole or levamisole (dogs)
Filaroides hirthi	Dogs	North America, Japan, Europe	Zinc sulfate flotation or Baermann technique or larvae in tracheal wash	Albendazole or fenbendazole
Crenosoma vulpis	Dogs	Worldwide	Larvae in tracheal wash or fecal Baermann technique	Fenbendazole or levamisole
Paragonimus kellicotti	Dogs and cats	Great Lakes, Midwest, southern United States	Eggs in tracheal wash or fecal sedimentation	Praziquantel or fenbendazole
Intestinal parasite migration*: ~*Toxocara canis*	Dogs	Worldwide	Ova on fecal flotation	Pyrantel pamoate; for larval migration use either fenbendazole or ivermectin

The most common radiographic finding in dogs with canine allergic bronchitis (eosinophilic bronchopneumopathy) is a diffuse, prominent, bronchointerstitial pattern. Forty percent of dogs have alveolar infiltrates (due to secondary pneumonia in some cases), and 26% have radiographic signs of bronchiectasis. A peripheral eosinophilia is present in about 60% of cases. Bronchoscopy typically reveals abundant yellow-green mucus or mucopurulent material, thickening with irregularities or polypoid changes to the mucosa, and exaggerated closure of the airways during expiration. Cytologic findings in fluid obtained from a bronchoalveolar lavage (BAL) or endotracheal wash (ETW) include more than 50% eosinophils in 87% of dogs and between 20% and 50% eosinophils in 13% of dogs.[15]

The mainstay of treatment for animals with this disease is glucocorticoids, with an induction dosage of prednisone of approximately 1 mg/kg q12h, although larger dogs often require lower dosages. Most dogs will relapse within months of discontinuing the steroids, but some dogs may remain disease free for years. A maintenance dosage of prednisone (0.25 to 0.5 mg/kg q48h) is suggested in an attempt to maintain remission. Other immunosuppressive drugs and inhaled medications have not been evaluated objectively for their efficacy in treating animals with this disease. Culture and sensitivity testing should be performed on the BAL or ETW fluid in order to rule out a secondary pneumonia. It is important to stress to the owner that this disease requires life-long management and there may be unwanted side effects from the long-term use of steroids.[12,15]

* Clinical signs may include cough, respiratory distress, and often a peripheral eosinophilia. Other intestinal parasites to consider in animals with allergic lung disease include *Ancylostoma caninum* and *Strongyloides stercoralis*.

20.7 PULMONARY INFILTRATES WITH EOSINOPHILS

PIE describes a spectrum of diseases that involve a type I hypersensitivity reaction occurring in the pulmonary parenchyma in response to various stimuli. PIE should be considered more of an “umbrella term” that encompasses several pulmonary diseases, all of which cause eosinophilic airway inflammation. The stimuli for this eosinophilic inflammation can include pulmonary or migrating parasites, heartworms, drugs, or inhaled allergens. One study showed that 65% of cases of PIE were caused by heartworm disease; however this predominance may vary depending on the animal's geographic location.[16] The disease tends to occur in adult dogs, with no known sex or breed predilection.

Although PIE appears to be allergic in nature based on the high numbers of eosinophils in the airways, it leads primarily to pulmonary parenchymal disease rather than airway disease. Affected dogs have classic symptoms of parenchymal disease, including respiratory distress with rapid, shallow breathing, coughing, and possibly cyanosis. Radiographically, a diffuse interstitial, bronchial, or alveolar pattern is apparent, and many dogs also have hilar lymphadenopathy. Bronchoscopy and BAL or ETW reveal a predominance of eosinophils within the airways. A peripheral eosinophilia is common, but its presence is dependent on the cause of the pulmonary eosinophilic inflammation. The morbidity and mortality in animals with PIE depends primarily on the underlying cause of PIE and whether the cause can be treated or removed. Given the heterogeneity of diseases represented by the term *PIE,* one should avoid this classification as an ultimate diagnosis and strive to uncover an underlying cause.[11,16]

20.8 FELINE BRONCHOPULMONARY DISEASE

Much like PIE, feline bronchopulmonary disease is a broad term that encompasses several disease processes. Although some cats may be truly allergic and asthmatic in nature, others may have chronic changes (chronic bronchitis) from prolonged and persistent irritation and inflammation to the lower airways related to nonallergenic stimuli.[2] Because these groups of cats will look very similar clinically and the etiology of feline bronchopulmonary disease is unknown, both diseases are presented here in detail. One should keep in mind, however, that most clinical cases of feline bronchopulmonary disease do not fit the true definition of allergic airway disease.

20.8.1 Pathogenesis

The pathogenesis of the feline bronchopulmonary inflammatory response appears variable. The response is difficult to predict because it has been reported that up to 30% eosinophils may be seen in the BAL or ETW fluid of healthy cats.[17] The cellular inflammatory response is only partially responsible for feline bronchopulmonary disease. Another important factor is lower airway hyperreactivity, which is defined as the ease with which airways narrow in response to a nonspecific stimulus. Although some cats may have inherently reactive airways to truly allergic stimuli, others may have a degree of airway responsiveness to extrinsic noxious stimuli. Feline patients have been reported to have exacerbations of signs associated with exposure to scented hair sprays, clay-based litters, scented air fresheners, or cigarette smoke. In some cases, simply removing the noxious stimulus from the environment may noticeably improve a cat's symptoms.[2]

20.8.2 Clinical Signs

Respiratory distress, with increased expiratory effort and rapid, shallow breathing, is a common manifestation of feline bronchopulmonary disease. Cats often display open-mouth breathing, and excessive coughing with severe tracheal sensitivity is common. Although the inflammation within the airways is typically a chronic problem, the episode of respiratory distress may appear acute and severe in nature. Airway narrowing caused by inflammation and bronchoconstriction in the lower airways frequently causes wheezes and a forced abdominal push during exhalation.[1,18]

Feline bronchopulmonary disease appears to be the most common cause of coughing in cats, although 16% of cases had no coughing in the history or during physical examination.[2,12] Seventy-five percent of cats in one study coughed during examination, and many also exhibited wheezing or sneezing. The Siamese breed is overrepresented in cats with lower airway disease. There is no known sex or age predilection.[2,3]

20.8.3 Laboratory Diagnostic Tests

Once the cat is stabilized, a complete blood count, biochemical analysis, and urinalysis should be performed to help rule out systemic diseases that could be causing respiratory distress (see Chapter 2, Patient Triage). These test results are typically normal in cats with feline bronchopulmonary disease, and it is a common misconception that they have a peripheral eosinophilia. In one study of cats with peripheral eosinophilia, only 9% were diagnosed with feline allergic airway disease.[2,3,19] A diagnosis of allergic airway disease in a cat with a peripheral eosinophilia should not be made without cytologic evidence demonstrating concurrent airway eosinophilia. A fecal examination will help rule in or rule out pulmonary parasites. A heartworm test is also important for any cat with labored breathing and evidence of bronchointerstitial disease. A bronchointerstitial pattern is the most persistent and chronic radiographic finding in feline heartworm disease, even without changes seen in the pulmonary vasculature.[12,20] Both feline antibody and antigen heartworm tests should be performed, because the amount of antigen can be extremely low or the antigen may be absent in some cats.[14]

20.8.4 Radiology

Thoracic radiographs are essential in a cat in respiratory distress. The cat should first be stabilized with oxygen, and other medications, if indicated. The radiographic appearance of feline bronchopulmonary disease can vary. The classic radiographic findings include an increase in bronchial densities, often described as *doughnuts, tram lines,* or *train tracks*. These terms describe the thickened bronchial walls viewed end-on or from the side. Other radiographic findings can include an increase in interstitial markings, an alveolar pattern, or hyperinflation of the lung fields with flattening of the diaphragm.[10-12] Alveolar infiltration and consolidation of the right middle lung lobe have been reported in 11% of cats with bronchopulmonary disease.[3] This radiographic appearance should not be mistaken for bronchopneumonia.

The severity of radiographic changes in cats with allergic airway disease varies, ranging from mild to severe, and does not necessarily correlate with the severity of symptoms or diagnostic test results.[23] A prognosis should therefore not be made based solely on radiographic changes.

20.8.5 Bronchoscopy

Bronchoscopy allows direct visualization of the trachea and bronchial tree. Cats with feline bronchopulmonary disease will often have thick mucus secretions in their lower airways, as well as hyperemic and edematous mucosa.[2,3] During bronchoscopy, a BAL should be performed. A BAL is preferred over a transtracheal wash because the BAL yields a cell population that is more representative of the lower airways and pulmonary interstitium. A BAL has also been shown to be more accurate than a transtracheal wash for the diagnosis of bacterial and mycotic infections of the lower airways.[21]

Fluid culture should be performed to rule out infectious causes of airway inflammation. A quantitative culture should be performed, with significant bacterial numbers indicating true bacterial infection. The bronchi of healthy cats are not considered sterile; thus a bacterial culture is generally considered significant only if the growth is greater than 2000 colony-forming units (cfus)/ml in cats. One study has shown that cats with feline bronchopulmonary disease have a significantly higher rate of mycoplasma colonization than that seen in cats with healthy airways.[2,3,17] The most predominant cell types found in bronchial washings of cats affected with bronchopulmonary disease are neutrophils and eosinophils. Dye and colleagues reported that moderately and severely affected cats had statistically significantly higher percentages of eosinophils, neutrophils, and combined neutrophils and eosinophils than did healthy cats. Mast cells, however, were found infrequently and represented up to 8% of all the cell types.[2] Moise and coworkers found that the predominant cell types in affected cats were eosinophils (24% of cats), neutrophils (33% of cats), macrophages (22% of cats), or a mixed cell population (21% of cats).[3] Clearly, cats with feline bronchopulmonary disease have variable cytologic findings, thus demonstrating why this disease is not routinely considered to be allergic in nature.

20.9 TREATMENT OF ALLERGIC AIRWAY DISEASE

20.9.1 Glucocorticoids

Although the causes of both canine and feline allergic airway disease are numerous, the medical treatment is similar because it is often difficult to remove the inciting cause (unless infectious in nature). The clinician must therefore attempt to control and dampen the clinical manifestations, which includes advising clients to remove inhalant irritants from the animal's environment, including such things as dusty litter, perfumes, aerosols, and cigarette smoke. Both drug therapy and irritant avoidance are necessary in most animals with allergic airway disease. Several options exist for medical treatment of these patients. Steroids, bronchodilators, and oxygen therapy are the mainstay of emergency therapy.[22] Steroids are used in emergent patients and for long-term therapy to decrease inflammation and resistance in the lower airways (Table 20-2).[23] Although steroids are generally very effective in decreasing airway resistance and inflammation, the common and often severe side effects of this class of drugs limit their practical use for long-term control of allergic airway disease.[24] Some inhalant steroids (e.g., fluticasone and flunisolide) are now being used in the clinical setting to control airway inflammation without the systemic side effects.[25] The efficacy of these medications has not been thoroughly evaluated (see Chapter 192, Aerosolized Medications).

Table 20-2 Commonly Used Medications and Dosages for the Treatment of Allergic Airway Disease in the Dog and Cat

Drug	Class and Mechanism	Indication	Dosage Recommended
Dexamethasone sodium phosphate	Glucocorticoid: long-acting	Parenteral steroid for emergency use	0.2 to 1 mg/kg IV or IM
Prednisone or prednisolone	Glucocorticoid: short-acting	Appropriate for maintenance use and alternate-day therapy	1 to 2 mg/kg PO q12h for 2 weeks, then taper over 2 to 3 months
Methylprednisolone acetate	Glucocorticoid: long-acting	Appropriate only for cases with problems in compliance	20 mg per cat IM q4-6wk
Aminophylline	Bronchodilator: methylxanthine	Not recommended orally because of the short half-life in dogs and cats	5 to 10 mg/kg PO q8h or 5 to 10 mg/kg IV q6-8h
Theophylline extended release (Inwood brand)	Bronchodilator: methylxanthine	Maintenance therapy	Cats: 15 mg/kg (tablets) or 19 mg/kg (capsules) PO q24 h/ Dogs: 10 mg/kg PO q12h
Terbutaline	Bronchodilator β_2-agonist	Parenteral or oral bronchodilator	0.01 mg/kg SC or IM q4h Cats: 1.25 mg PO q12h Dogs: 2.5 mg PO q8h

IM, intramuscular; *IV,* intravenous; *PO,* per os; *SC,* subcutaneous.

20.9.2 Bronchodilators

Two classes of bronchodilators can be used to manage allergic airway disease in veterinary patients. These include methylxanthines (theophylline, aminophylline) and selective β_2-receptor agonists (terbutaline or albuterol). Parenterally administered terbutaline has a rapid onset of action and is most commonly given to animals in acute, severe respiratory distress. Because β-agonist drugs may cause tachycardia or tachyarrhythmias in some animals, the clinician should attempt to rule out cardiac disease before administering these medications.[26] Inhaled β-agonist therapy is also an option for inpatient or outpatient therapy of allergic airway disease and may carry fewer side effects (see Chapter 192, Aerosolized Medications). Methylxanthine drugs may be preferable for long-term bronchodilation because tolerance to the β-agonist drugs may occur and subsequently decrease their efficacy in emergency situations. The Inwood brand of theophylline results in the most reliable and appropriate pharmacokinetics in dogs.[27]

Antihelminthic medications are recommended routinely for animals with allergic airway disease. Although bronchoscopy and BAL washings offer the best chance of diagnosing parasitic allergic airway disease, migrating larvae and primary pulmonary parasites can be missed with these diagnostic tools.[11] Deworming protocols are generally very safe and can effectively cure animals with parasitic allergic airway disease.

20.9.3 Miscellaneous Drugs and Other Therapies

Because of the potent side effects of many steroids, other drugs have been used empirically for the treatment of allergic airway disease. There are no controlled, in vivo studies that demonstrate the efficacy of these medications; however, they are sometimes prescribed when other medications appear unsuccessful. Cyclosporine is an immunosuppressant that specifically inhibits the T-helper cells of the immune system. There is evidence that the T-helper cells are a primary component of the allergic immune response.[24] Cyclosporine has been shown to block inflammatory changes associated with experimental asthma in cats; however, it has not been evaluated in 85
naturally occurring cases of allergic airway disease and its side effects may preclude its use in routine treatment.[28] 86
Many human asthmatics are now treated with therapies such as leukotriene receptor blockers (montelukast and zafirlukast) or inhibitors of the enzyme 5-lipoxygenase (zileuton), which is responsible for the formation of leukotrienes themselves.[29] Cysteinyl leukotrienes do not appear to be important mediators of bronchoconstriction in cats, and the one veterinary study evaluating these medications did not show efficacy using a lipoxygenase blocker in a model of experimentally induced feline allergic airway disease.[30]

Cyproheptadine has also been suggested for use in cats with allergic airway disease. It is a serotonin receptor antagonist that inhibits feline airway smooth muscle contraction in vitro. Oral administration (2 mg q12h) was associated with a reduction in airway hyperreactivity in a subpopulation of cats with experimentally induced asthma, although there is some evidence to suggest that higher dosages (i.e., 8 mg q8-12h) may be more appropriate.[30] It has yet to be determined whether cyproheptadine will work in vivo in cats with airway disease. Serotonin does not appear to play a role in smooth muscle contraction in human or equine species.[31]

20.10 PROGNOSIS

The prognosis for small animals with allergic airway disease is variable and depends on the cause, chronicity, and continued exposure to irritants. The overall clinical picture can be exacerbated by concurrent underlying cardiac or other respiratory disease. Feline bronchopulmonary disease in cats is often a chronic disorder, one that will manifest with either persistent signs or episodic flare-ups. Patient morbidity is high in affected cats because of the chronicity of the disease.

20.11 SUGGESTED FURTHER READING*

JE Bach, B KuKanich, MG Papich, et al.: Evaluation of the bioavailability and pharmacokinetics of two extended release theophylline formulations in dogs. *J Am Vet Med Assoc*. **224**, 2004, 1113, *Demonstrates the pharmacokinetics of theophylline in the dog and shows that only one of the brands studied has predictable pharmacokinetics*.

JA Dye, BC McKiernan, EA Rozanski, et al.: Bronchopulmonary disease in the cat: historical, physical, radiographic, clinicopathologic, and pulmonary functional evaluation of 24 affected and 15 healthy cats. *J Vet Intern Med*. **10**, 1996, 385, *Prospective study describing the common clinical findings in cats with feline bronchopulmonary disease*.

PA Padrid: Use of inhaled medications to treat respiratory diseases in dogs and cats. *J Am Anim Hosp Assoc*. **42**, 2006, 165, *Review of what is currently known in veterinary small animal medicine regarding the use of inhaled medications and provides dosages commonly used in the treatment of feline bronchopulmonary disease*.

* See the CD-ROM for a complete list of references.

21 Chapter 21 Pulmonary Edema

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21.1 Key Points

- Pulmonary edema is a common cause of dyspnea in dogs and cats.
- Two main pathophysiologic forms exist: high-pressure edema and increased permeability edema.
- Hydrostatic pressure is an important pathologic mechanism in both forms of edema.
- Cardiogenic edema and fluid overload are the most common forms of high-pressure edema.
- Decreased colloid osmotic pressure (COP) within the intravascular space is rarely a sole cause of pulmonary edema.
- Pulmonary capillary pressure modification is important in management of both pathophysiologic forms.
- Fluid therapy should be administered with caution in all patients with pulmonary edema.
- The prognosis for animals with pulmonary edema varies depending upon the underlying cause.

21.2 INTRODUCTION

Pulmonary edema is the accumulation of extravascular fluid within the pulmonary parenchyma or alveoli. The two main pathophysiologic forms are high-pressure edema (due to increased pulmonary capillary hydrostatic pressure) and increased permeability edema (due to damage of the microvascular barrier and alveolar epithelium in more severe cases). Pulmonary edema is a relatively common disease process in veterinary patients that can be rapidly life threatening.

21.3 PATHOPHYSIOLOGY

In normal tissues, transvascular fluid fluxes are determined by Starling forces. The amount of flow is dependent on a number of variables: the capillary hydrostatic pressure, interstitial hydrostatic pressure, capillary colloid osmotic pressure (COP), interstitial COP, and the reflection and filtration coefficients for the tissues.[1] 87

The filtration coefficient is a measure of fluid efflux from the vasculature of specific tissues and is dependent on the capillary surface area and hydraulic conductivity. The reflection coefficient indicates the relative permeability of the membrane to protein. Tissue safety factors protect tissues against the deleterious effects of edema. In normal tissues, extravasation of low-protein fluid results in a fall in interstitial COP, which results in preservation of the COP gradient, thereby protecting against further fluid extravasation.[2] Other safety factors in nondistensible tissues include increased interstitial hydrostatic pressure and increased driving pressure for lymphatic flow (which can increase up to 10 times normal).

The pulmonary capillary endothelium is relatively permeable to protein compared with other tissues, so the effective COP gradient that can be generated between the intravascular space and pulmonary interstitium is lower than in other tissues. Consequently, increased lymphatic flow is largely responsible for protecting against edema in the lung,[3] and hypoproteinemia causing a decrease in COP rarely results in pulmonary edema. Pulmonary edema occurs when the rate of interstitial fluid formation overwhelms the protective fluid clearance mechanisms. Due to the lower COP gradient, hydrostatic pressure is the main determinant of fluid extravasation and edema formation in the lungs,[4] hence the rationale for using hydrostatic pressure modulators in the treatment of all forms of pulmonary edema. The pulmonary ultrastructure is designed to protect gaseous diffusion. Most interstitial fluid flow is on the side of the capillary opposite to that where gas exchange occurs, and the distensibility of the lung tissue increases toward the peribronchovascular region. This results in initial fluid accumulation in areas not used for gas exchange.[5]

High-pressure edema forms as a result of increasing pulmonary capillary pressures, leading to fluid extravasation that eventually overwhelms the lymphatic removal capacity. Fluid flows initially toward the peribronchovascular interstitium, then distends all parts of the pulmonary interstitium, and eventually spills into the airspaces at the junction of the alveolar and airway epithelia.[4] In many animals with cardiogenic edema, the increase in pressure occurs gradually, and overt edema may develop over a period of months; however, if there are acute increases in hydrostatic pressure (e.g., chordae tendineae rupture), then edema will form rapidly.

Increased permeability edema occurs secondary to injury to the microvascular barrier and alveolar epithelium, resulting in extravasation of fluid with a high protein content.[4] The protective fall in COP is thereby diminished, so the hydrostatic pressure becomes the main determinant of edema formation. Interstitial fluid accumulation can then occur at even lower hydrostatic pressures, and relatively small rises in pressure can result in greater edema formation. In more severe cases in which the alveolar epithelium is also damaged, a direct conduit may form in the intravascular space, and interstitial edema progresses to alveolar flooding. This occurs rapidly and explains the greater severity and fulminant course of increased-permeability edema compared with hydrostatic edema.

Although the lymphatic system plays a major role in limiting interstitial fluid accumulation, it has only a minor role in the clearance of pulmonary edema. Most fluid is mobilized to the bronchial circulation, probably because most fluid tends to accumulate in the peribronchovascular areas.[6] The rate of resolution depends on the fluid type, with pure water being reabsorbed much more rapidly than fluid containing macromolecules and cells.

21.4 CLINICAL PRESENTATION

Pulmonary edema results in reduced oxygenation, usually as a result of ventilation-perfusion mismatching; therefore most animals have symptoms of respiratory distress. Some of these patients are extremely fragile, so a risk-benefit assessment should be considered before even performing a physical examination. Oxygen should be given to all patients with respiratory distress, and the benefits of giving a patient time to recover in a quiet, oxygen-enriched environment cannot be overstressed (see Chapter 19, Oxygen Therapy). Initial diagnostic evaluation should be directed toward identifying the severity of the respiratory disease and the underlying cause. Historical information can be useful in some cases, such as smoke inhalation, choking, or a previous diagnosis of congestive heart failure. Neurogenic pulmonary edema may be suspected in animals that have dyspnea after head trauma, upper respiratory tract obstruction, or electric shock.

As with many conditions, the severity is often inversely proportional to the duration of clinical signs. Although typically associated with pulmonary edema, crackles are not heard in all cases; however, most patients will have either loud lung sounds or crackles. Crackles are particularly difficult to hear in patients with rapid respiratory rates and low tidal volumes. Careful auscultation may allow the abnormal lung sounds to be localized to one region and this may aid in the diagnosis, such as a cranioventral distribution with aspiration pneumonia and occasionally a perihilar distribution with cardiogenic pulmonary edema (primarily in the dog).

21.4.1 High-Pressure Edema

21.4.1.1 Cardiogenic Edema

Cardiogenic pulmonary edema is the most common form of high-pressure edema.[7] It occurs as a result of left-sided congestive heart failure. Cardiac disease is often chronic, and in dogs there is usually a history of clinical signs consistent with heart disease: cough, exercise intolerance, and usually a heart murmur. Acute onset of signs may be seen, particularly if there has been a precipitating event such as stress. Cats often have no premonitory clinical signs. Due to the chronic progression of heart disease, compensatory mechanisms result in fluid retention to maintain cardiac output and, although beneficial in the short term, this eventually leads to signs of congestion which in its most life-threatening form is pulmonary edema.

As a result of chronic increases in blood volume, the capillary pressure at which edema forms is higher than in the normal dog or cat. In severe cases blood vessel rupture may occur, leading to a serosanguineous appearance of secretions, as evidenced by pink frothy sputum. Fortunately only a few common diseases cause cardiogenic pulmonary edema, and signalment can be extremely useful in forming a differential diagnosis list. Middle-aged, large breed dogs tend to have dilated cardiomyopathy, whereas the smaller breeds tend to have mitral valve disease. Cats are more prone to the myocardial diseases, with hypertrophic, thyrotoxic, and restrictive cardiomyopathies seen most commonly.[7]

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21.4.1.2 Fluid Therapy

Fluid therapy is an uncommon cause of pulmonary edema without preexisting heart or lung disease, due to the effective safety mechanisms within the lung. However, fluid therapy may cause rapid increases in hydrostatic pressure in animals with preexisting (although asymptomatic) heart disease, leading to pulmonary edema. Experimental studies have demonstrated that dogs are able to cope with large volumes: dosages of 360 ml/kg of crystalloid over 1 hour were given before severe fluid overload was seen.[8] Cats are less able to cope with large volumes, especially those with renal failure, cardiac insufficiency, or lung disease. Synthetic or natural colloid products and hemoglobin-based oxygen-carrying solutions cause much more volume expansion than crystalloids. Approximately 5 times the amount of colloid is retained within the intravascular space, so appropriate reductions in fluid administration rates and dosages should be made, especially in cats. When there are other risk factors such as systemic inflammation, pulmonary parenchymal disease, or hypoalbuminemia, fluid therapy may readily lead to pulmonary edema.

21.4.2 Increased-Permeability Edema

An increase in permeability is caused by direct injury to the microvascular barrier or alveolar epithelium by chemical damage and inflammatory mediators. Patients with systemic inflammatory response syndrome (SIRS) and diseases associated with systemic vasculitis are at increased risk of developing an increased-permeability edema. Infectious diseases that cause parenchymal inflammation can also cause increased-permeability edema. Acute respiratory distress syndrome (ARDS) is the most severe form of increased-permeability edema and is extremely difficult to manage. Clinical experience suggests that survival rate is low, although no studies have been performed to confirm this. Both SIRS and ARDS occur secondary to other disease processes, which may be primarily in the lung or in another organ system, for example, sepsis, pancreatitis, pneumonia, severe tissue trauma, immune-mediated disease, and metastatic neoplasia (see Chapters 11 and 24, Systemic Inflammatory Response Syndrome and Acute Lung Injury and Acute Respiratory Distress Syndrome, respectively).[9] Because these conditions often are difficult to manage, the clinician should be aware of the differential diagnoses for dyspnea in affected patients and act rapidly and aggressively if dyspnea occurs.

Other causes of increased-permeability edema include pulmonary thromboembolism (see Chapter 27, Pulmonary Thromboembolism), ventilator-associated lung injury (see Chapter 26, Ventilator-Associated Lung Injury), toxic lung injury such as volatile hydrocarbons and cisplatin in cats, and smoke inhalation (see Chapter 28, Smoke Inhalation). A number of chemical irritants in smoke can directly injure the respiratory tract and inactivate surfactant, causing a combination of atelectasis and increased-permeability edema.

21.4.3 Mixed Cause Edema

There are a number of other causes of pulmonary edema in which the pathophysiology is incompletely understood and that are probably due to a combination of hydrostatic and increased-permeability edema. Neurogenic edema is typically seen after head or neck trauma, submersion injuries, seizures, electrocution, and upper respiratory tract obstruction. Most affected dogs are young (<1 year) and the initiating cause may be trivial, such as a pull on a choke chain. Older dogs tend to have a more serious underlying disease, such as laryngeal paralysis or seizures. Signs of respiratory distress are seen immediately after the incident, and the prognosis for the resolution of edema depends on the inciting cause but is typically good, especially in younger dogs. Reexpansion edema has been reported in dogs and cats after acute reexpansion of chronically collapsed lung lobes.[10] Suggested mechanisms include decreased surfactant levels in collapsed lung tissue, negative interstitial pressure, and oxygen free radical formation and reperfusion injury.

21.5 DIAGNOSTIC TESTS

Thoracic radiographs are the most useful initial test to identify the cause of dyspnea; however, they can be highly stressful and should be avoided in the most severely dyspneic patient until initial stabilization with empiric therapy has been attempted. Most dogs will tolerate a quick lateral radiograph. Cats should not be placed in lateral recumbency because most find this extremely stressful. Most cats will tolerate sitting in sternal recumbency.

Equipment should be made ready in advance and oxygen supplementation should be available before attempting to radiograph these patients. The distribution of the alveolar pattern can be helpful in discriminating between cardiogenic (Figure 21-1, *A*) and noncardiogenic (see Figure 16-2) edema, but nearly all causes of edema can cause a diffuse alveolar pattern. Cardiogenic edema in dogs is typically seen in the perihilar region. In cats, however, there can also be a patchy, almost nodular, diffuse alveolar pattern (Figure 21-2). Pulmonary veins that are more distended than the pulmonary arteries may also be seen in some cases. A dorsocaudal alveolar pattern suggests neurogenic edema, whereas a cranioventral pattern is suggestive of aspiration pneumonia. A brief echocardiogram may reveal an enlarged left atrium, which raises the likelihood of congestive heart failure. In dyspneic patients, positioning may be challenging, and dyspneic animals should not be stressed excessively to obtain an echocardiogram.

Arterial blood gas analysis or pulse oximetry may be used to provide objective evidence of hypoxemia; however, they are not essential for stabilization and cause too much stress to perform in cats or very small dogs (see Chapter 208, Blood Gas and Oximetry Monitoring). Pulse oximeters are often unreliable, especially in conscious patients that are moving or have darkly pigmented skin. Pulse oximetry measurements are accurate only when a reliable pulse waveform is seen. Arterial blood gas analyzers are becoming increasingly available and, with practice, arterial blood sampling is a relatively easy technique to master. Sampling from the dorsal metatarsal artery is less stressful than from the femoral artery and can be performed even in standing dogs. Arterial blood gas analysis also allows calculation of the alveolar-arterial gradient, which typically is increased in all cases of pulmonary edema, except in the very early stages.

21.6 TREATMENT

21.6.1 Oxygen Therapy

Treatment of pulmonary edema depends on the underlying cause. No therapy is uniformly effective. Oxygen 88 89 supplementation should be provided by the least stressful means, as with all dyspneic patients, to increase arterial oxygen content and tissue oxygen delivery. Patients should be subjected to minimal stress, and movement should be limited to prevent increases in oxygen demand. Dyspneic animals should never be forcibly restrained. An oxygen cage is ideal following initial evaluation (if available), but mask, flow-by, or nasal cannula is also effective (see Chapter 19, Oxygen Therapy). Positive-pressure ventilation (PPV) may be indicated in patients that cannot maintain a hemoglobin saturation above 90% or a partial pressure of arterial oxygen (PaO_2) over 60 mm Hg with noninvasive methods of oxygen supplementation or those with evidence of hypoventilation ($PaCO_2$ >55 to 60 mm Hg) (see Chapter 213, Basic Mechanical Ventilation). If impending respiratory fatigue is a concern, PPV should be considered before there is significant deterioration (see Chapter 19, Oxygen Therapy). There is contradictory evidence in the literature regarding the effects of PPV on the resolution of pulmonary edema; PPV may help to resolve pulmonary edema in some situations, but slow it in others.[11,12] There can be significant morbidity associated with PPV, so careful case-by-case consideration should be made before commencing ventilation.

Figure 21-1 **A,** Lateral radiograph of a dog (Doberman Pinscher) showing marked perihilar alveolar infiltrates, an enlarged cardiac silhouette, and left atrial enlargement. This dog had severe congestive heart failure secondary to dilated cardiomyopathy. **B,** Lateral radiograph of the same dog 3 days later after intensive diuretic, positive inotropic, and vasodilator therapy (furosemide, dobutamine, pimobendan, and nitroprusside). There is marked improvement in the alveolar pattern, although mild perihilar infiltrates are still present.

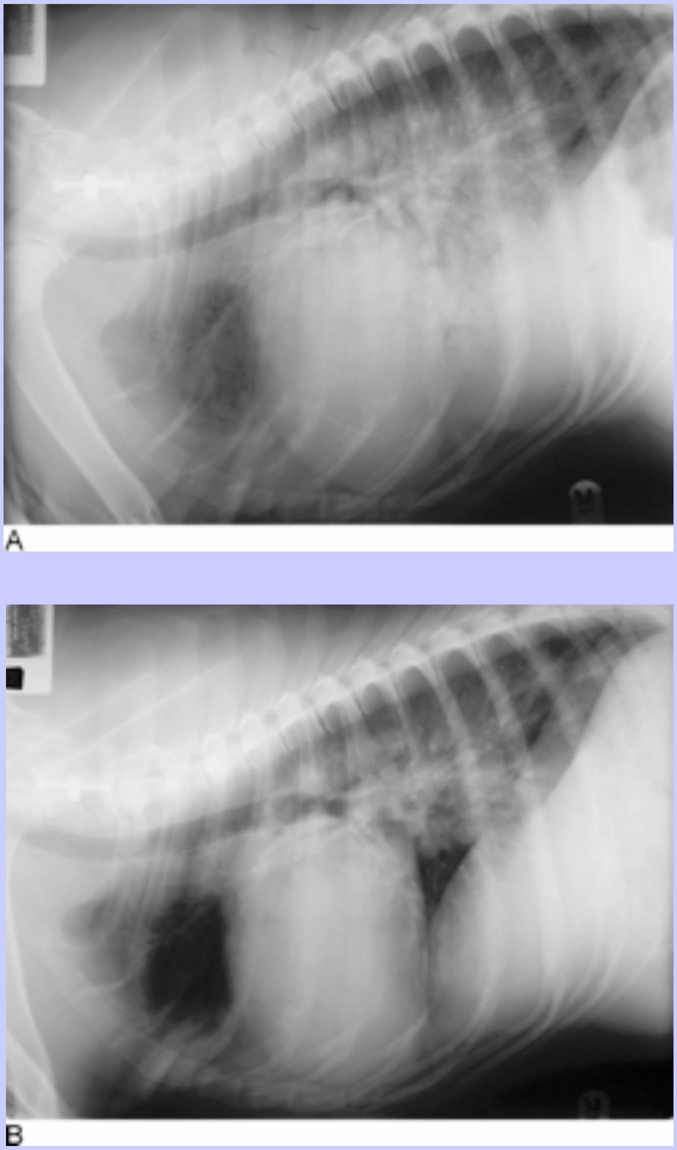
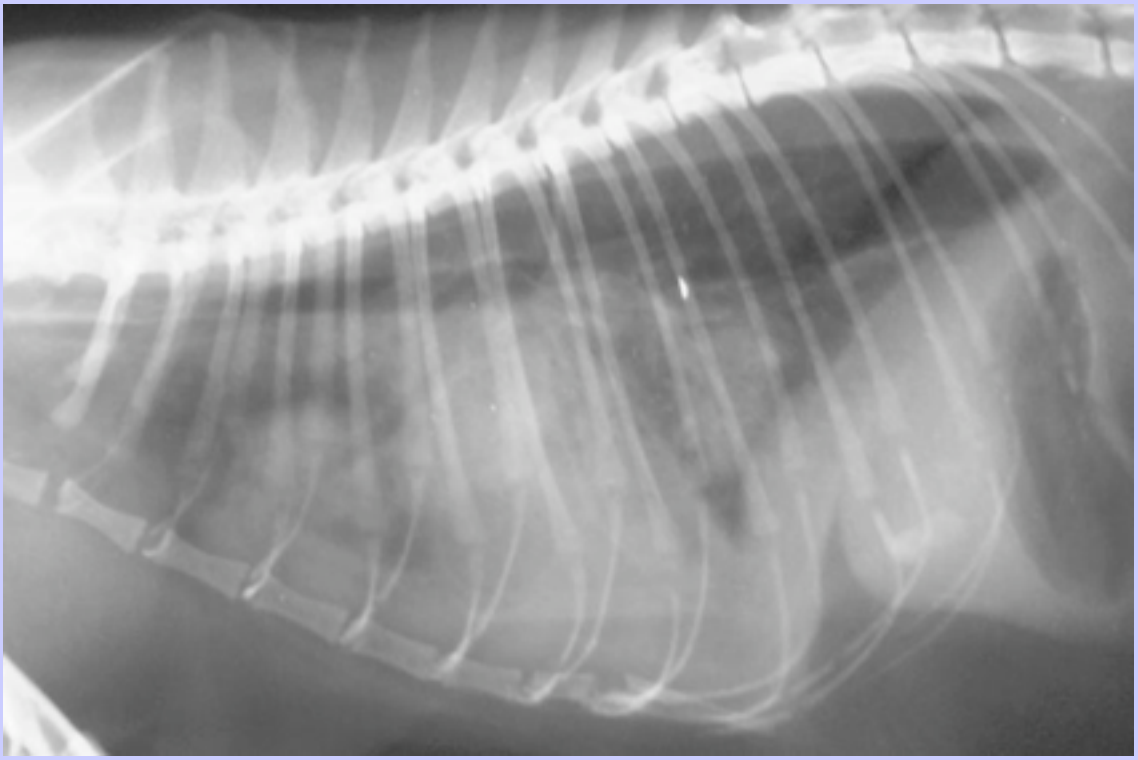


Figure 21-2 Lateral radiograph of a cat with congestive heart failure. Note the enlarged cardiac silhouette and widespread patchy alveolar infiltrates.



Body position can also be important. Sternal recumbency aids with gas exchange, probably by reducing atelectasis. In animals with unilateral disease it is preferable initially to place the patient with the affected lung lobe down if the animal will not tolerate sternal recumbency. In some patients placing the more severely affected lung uppermost can precipitate severe hypoxemia.

21.6.2 Medical Therapy

The key to managing cardiogenic pulmonary edema is the reduction of pulmonary capillary pressures by reducing preload. Promotion of forward flow is also important in patients with large regurgitant fractions. The drugs used can be split into two groups, diuretics and vasodilators. Furosemide is the most frequently used diuretic and is particularly useful because of its rapid onset of action (see Chapter 180, Diuretics). Excessive use can cause hypovolemia as a result of an excessive reduction in preload. Typically furosemide is used to effect at dosages of 1 to 4 mg/kg IV or IM (up to 8 mg/kg in the dog) as needed (up to every 30 to 60 minutes) until the respiratory status is stabilized and evidence of pulmonary congestion is improved. The frequency and dosage are subsequently reduced. In very severe cases this may be hourly initially, although in most cases every 3 to 4 hours is adequate.

There is evidence that furosemide acts as a pulmonary vasodilator and bronchodilator, and causes an increase in COP secondary to hemoconcentration. These changes, in combination with the resultant reduction in pulmonary hydrostatic capillary pressure, may assist with alveolar fluid reabsorption.[13-15] Concerns have been expressed about reduced mucociliary clearance due to excessive dehydration of secretions, but in life-threatening situations this is not an immediate concern. Constant rate infusions (CRIs) are more effective in promoting fluid excretion than intermittent boluses in humans with congestive heart failure,[16] and experimental studies in healthy greyhounds have shown better diuresis with a CRI than with bolus injection.[17] Nevertheless, patients with severe pulmonary edema need a more rapid effect; bolus therapy is recommended.

Vasodilators are less commonly used but can prove beneficial in many cases. A number of drugs are available, but in acute situations the most useful group are the nitric oxide donors, which include nitroprusside and glycerol trinitrate (nitroglycerin). These drugs act rapidly to cause vasodilation, thereby reducing preload and afterload (see Chapters 178 and 179, Antihypertensives and Nitroglycerin, respectively). Nitroprusside is a balanced vasodilator that may cause hypotension due to arteriolar dilation. It has a short half-life and is therefore administered intraveneously as a CRI. Nitroprusside should be used with extreme caution in hypotensive patients because the general goal with therapy is to reduce the mean arterial pressure (or systolic blood pressure) by 10 to 15 mm Hg from the baseline pressure. In hypotensive patients, nitroprusside should not be used without a positive inotrope; however, there is evidence to suggest that even in patients with severe left ventricular dysfunction, nitroprusside is associated with beneficial cardiopulmonary effects.[18] Animals should be monitored carefully for clinical signs of hypotension, ideally with invasive blood pressure monitoring, although this may not be possible in all cases. In addition to its hypotensive effects, nitroprusside may cause a reduction in hypoxic pulmonary vasoconstriction, thereby increasing ventilation-perfusion mismatch. A reflex tachycardia is also commonly seen. Because nitroglycerin is mainly a venodilator, minimal hypotension or tachycardia is seen with this drug, so it is safe in most cases. Nitroglycerin is available as a paste, which is applied to hairless areas such as the axilla or ear flap. Empiric doses of ¼ inch in cats and ¼ to 2 inches per dog are recommended and can be repeated every 6 to 8 hours. Tachyphylaxis occurs rapidly and the drug may have reduced efficacy after as little as 24 hours. Care should be taken with application: gloves should be worn and the ointment should be rubbed in well. Headaches are a common side effect in people.

Other drugs that have been of benefit in experimental models include β_2-agonists, such as terbutaline.[19,20] These act via cyclic adenosine monophosphate (cAMP)[19] to increase fluid reabsorption from the alveolar space. Caution should be exercised when using β_2-agonists in cats with pulmonary edema, however, because these drugs may worsen cardiac function in patients with hypertrophic, restrictive, or hyperthyroid-induced cardiomyopathy. Phosphodiesterase inhibitors such as pimobendan also increase cAMP levels and these drugs may also prove useful in the management of pulmonary edema, although scientific data are lacking. Their cardiovascular effects, vasodilation and positive inotropy, may prove beneficial for the treatment of cardiogenic pulmonary edema.

Because hydrostatic pressure influences both increased hydrostatic pressure and increased permeability edema, pressure modification is indicated in all cases of pulmonary edema. Most patients with noncardiogenic edema do not respond as well as those with cardiogenic edema to medical interventions to decrease hydrostatic pressure (Figure 21-1, *B*). However, some improvement may be seen, and in most cases these drugs are safe when used with caution. Large-scale clinical studies are lacking, however, and most experimental data point toward therapeutics that modulate hydrostatic pressure for the management of noncardiogenic edema.

21.6.3 Fluid Therapy

Because the hydrostatic pressure gradient is so important in the pathogenesis of pulmonary edema, it seems prudent to restrict fluid administration to these patients. In all cases, the decision to restrict intravenous fluid administration should be balanced against the risks of compromised renal function and multiple organ failure. The pulmonary, microvascular barrier is relatively permeable to protein[21] and therefore natural or synthetic colloids such as albumin or hetastarch, respectively, may equilibrate rapidly across the endothelial space. If there is increased permeability such that most of these molecules may extravasate, colloid therapy may lead to worsening of the pulmonary edema, which will resolve slowly due to slow clearance of macromolecules from the alveolar space. Because there is no way of clinically determining the permeability, one has to rely on response to therapy. A trial dose of colloid may be administered cautiously in animals suspected of having increased vascular permeability.

21.7 PROGNOSIS

Due to the diversity of causes of pulmonary edema, general statements about prognosis cannot be made. Usually when there is no serious underlying disease, the prognosis for resolution is good. However, when there is evidence of multisystemic disease and severe increased permeability edema, the prognosis is guarded at best. The prognosis for cardiogenic edema is related to the severity of the underlying disease; some dogs with mitral valve disease may survive for years after diagnosis of failure, whereas the prognosis for dogs with dilated cardiomyopathy may be poor. In cats, the prognosis with congestive heart failure is less favorable and few of these animals live beyond 1 to 1½ years from the time of diagnosis. Those that respond well to initial treatment with furosemide and vasodilators seem to have a slightly better prognosis than those whose disease is difficult to control.

The outcome in animals that require PPV is generally poor, although financial concerns are often involved in many of these decisions. Nevertheless, survival rates are low.[22,23]

21.8 SUGGESTED FURTHER READING*

D Hughes: Pulmonary edema. In W Wingfield, M Raffe (Eds.): *The veterinary ICU book*. 2002, Teton NewMedia, Jackson Hole, WY, *Useful manual covering veterinary emergency and critical care*.

LG King, JC Hendricks: Use of positive pressure ventilation in dogs and cats: 41 cases (1990-1992). *J Am Vet Med Assoc*. **204**, 1994, 1045, *The first large case series on ventilation in dogs and cats. Overall survival rate was 39%, with a much lower survival rate in those cases ventilated for primary parenchymal disease (20%) compared with 57% in ventilatory failure*.

JA Lee, KJ Drobatz, MW Koch, LJ King: Indications for and outcome of positive-pressure ventilation in cats: 53 cases (1993-2002). *J Am Vet Med Assoc*. **226**, 2005, 924, *A large case series of positive-pressure ventilation in cats. This series reports a low overall survival (15%), which was lower in cats with primary parenchymal disease. The survival rate in cats appears to be lower than that in dogs*.

C Parent, LG King, LM Walker, et al.: Clinical and clinicopathological findings in dogs with acute respiratory distress syndrome: 19 cases (1985-1993). *J Am Vet Med Assoc*. **208**, 1996, 1419, *Description of clinical and pathologic findings in dogs with a histopathologic diagnosis of ARDS. There is a sister article on treatment and respiratory function in the same issue*.

* See the CD-ROM for a complete list of references

22 Chapter 22 Pneumonia

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22.1 KEY POINTS

- Pneumonia is an inflammation of the lung parenchyma that is often secondary to an underlying disorder in dogs and cats.
- Complete blood count results are neither sensitive nor specific, and the white blood cell count cannot be used reliably to confirm or rule out pneumonia.
- Many patients with bacterial pneumonia (dogs: 53%; cats: 74%) are afebrile. Coughing is usually absent in cats with pneumonia (92% of cases do not cough), but dyspnea is common (49%).
- Obtaining three-view thoracic radiographs, avoiding overexposure or underexposure, and carefully examining all lung fields on all thoracic radiographs are important measures for detecting pneumonia radiographically.
- An endotracheal or transtracheal wash with culture and sensitivity testing is often useful for determining the etiologic agent(s).
- Long-term antibiotic therapy is indicated for infectious pneumonia.
- Appropriate treatment and supportive care will maximize success. Severe sepsis and multiple organ dysfunction are poor prognostic indicators.

22.2 INTRODUCTION

Pneumonia is an inflammation of the lung parenchyma.[1,2] It occurs chiefly in response to inhalation of infectious agents (bacteria, viruses, fungi, protozoa, parasites) either as a primary disorder or secondary to a predisposing disturbance in the lungs. Less common causes of pneumonia include idiopathic eosinophilic pneumonia, secondary to inhaled allergens or a hematogenous infection, and endogenous lipid infiltration.[1] Pneumonia that occurs as a result of inhalation of foreign substances or materials is described in Chapter 23, Aspiration Pneumonitis and Pneumonia. The focus of this chapter is infectious pneumonia.

22.3 CLINICAL PRESENTATION

22.3.1 Initial Evaluation

Critically ill animals with pneumonia require rapid identification and treatment. A soft cough, mild dyspnea, and nonspecific signs of lethargy and inappetence may be noted as the earliest manifestations in some dogs and cats. However, many patients with pneumonia show no respiratory signs (e.g., 36% of cats).[3] The spectrum of clinical signs ranges from none (the diagnosis is made incidentally on thoracic radiographs) to life-threatening dyspnea and impending cardiorespiratory arrest. Therefore pneumonia may be suspected at one of several points in the evolution of a case: when clinical signs are noted, when predisposing causes are identified, or when characteristic findings are apparent on thoracic radiographs.

22.3.2 History

Elements of a patient's history that should raise the clinician's index of suspicion for pneumonia are numerous. Broadly, historical clues include respiratory signs (cough, increased respiratory effort, purulent nasal discharge), systemic signs including lethargy and inappetence, and signs associated with predisposing or underlying causes (Table 22-1). Approximately 36% to 57% of dogs with pneumonia are found to have a concurrent predisposing disorder.[4,5] Geographic location and travel history may reveal important details to consider in cases suspected of having fungal or parasitic disease.

22.3.3 Physical Examination

Physical abnormalities in patients with pneumonia often are nonspecific beyond respiratory signs.[1,5] Demeanor may be normal, with some patients showing a bright and alert disposition despite having pneumonia, or abnormal, with lethargy and depression predominating. Inappetence, weight loss, and signs attributable to an underlying disorder are common. Respiratory signs are rarely sensitive or specific. For example, dyspnea occurs with moderate or severe pneumonia, but is absent in mild cases. The cough of a patient with pneumonia may be moist or dry, and tracheal pressure may elicit a cough in some pneumonia patients and not in others. Most dogs with pneumonia (>90%) do have abnormally loud breath sounds, crackles, or wheezes on pulmonary auscultation[6]; however, these findings are nonspecific and do not allow differentiation from other causes of dyspnea (pulmonary edema, pulmonary hemorrhage). In contrast to dogs (47%),[6] cats with infectious pneumonia rarely cough (8%).[3] Mucopurulent nasal discharge may or may not be present in either species. Fever is a highly inconsistent finding in both species, and pneumonia can be neither confirmed nor ruled out on the basis of body temperature. Animals with fungal, viral, parasitic, or protozoal pneumonia may have multisystem involvement (e.g., bone, intestinal tract, lymph nodes). Overall, pneumonia is suspected in an animal when one or more compatible signs are noted in the history and physical examination, especially in a patient with a predisposing condition (see Table 22-1).

22.4 DIAGNOSTIC TESTING

Evaluation of patients suspected of having pneumonia is centered on diagnostic imaging and sampling respiratory

secretions. Thoracic radiography remains the routine imaging test of choice. The characteristic finding is alveolar opacification. Air bronchograms, silhouetting of lung(s) with the heart, and consolidation, with or without interstitial patterns, are typically present with an asymmetric distribution (Figure 22-1). The alveolar pattern of pneumonia often is visualized more clearly in one radiographic view than in another. For example, a left lateral thoracic radiograph will allow optimal visualization of the right lung fields. Therefore, three-view thoracic radiography (a dorsoventral or ventrodorsal projection and both lateral projections) is recommended in all pneumonia suspects, in order to minimize false-negative results and underdiagnosis. Computed tomography may also be beneficial in animals with complicated pulmonary disease or with those suspected of having foreign body–associated pneumonia, to assist in the approach to exploratory thoracostomy or lung biopsy.

Table 22-1 Factors Predisposing to or Associated With Pneumonia in Dogs and Cats

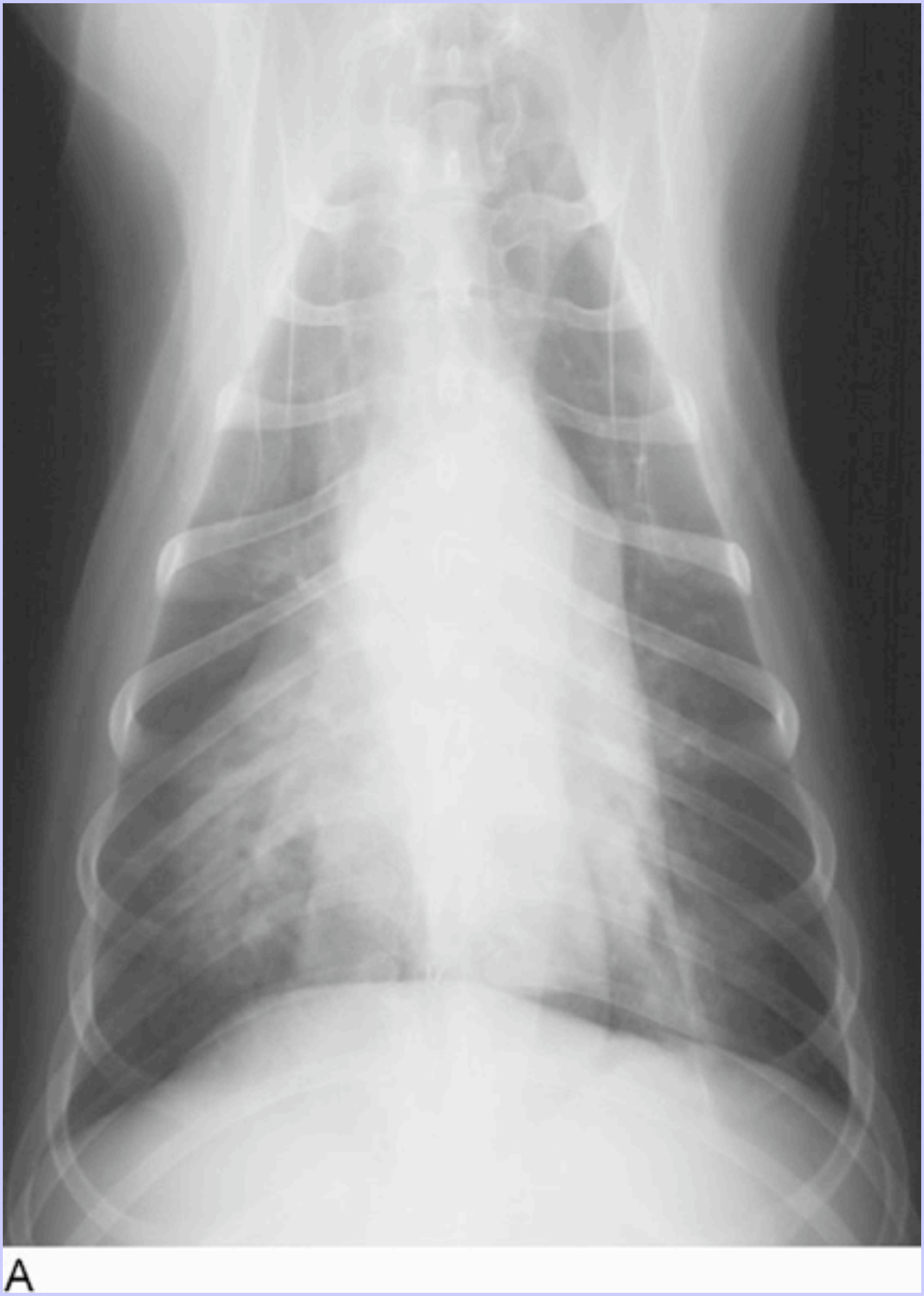
Factor	Comment
Impaired patient mobility	
Unconsciousness (natural, or via general anesthesia)*	Attenuation, loss of reflexes (gag, cough)
Mechanical ventilation	Natural defense mechanisms of the upper airway bypassed by intubation and mechanical ventilation; normal movement and coughing prevented Regurgitation or aspiration of oropharyngeal bacteria may contribute
Weakness, paresis, paralysis*	—
Upper airway disorders	
Laryngeal mass or foreign body*	Successful laryngeal examination possible using only a bright light source (Finnoff transilluminator) and without sedation in patients with laryngeal disorders, especially laryngeal paralysis
Laryngeal paralysis*	
Laryngeal or pharyngeal surgery*	Aspiration pneumonia (without overt clinical signs)—a common postoperative complication in animals with laryngeal paralysis (see Chapter 23, Aspiration Pneumonitis and Pneumonia)
Regurgitation syndromes	
Esophageal motility disorder*	Dynamic esophagram (barium swallow) required for diagnosis Important if other tests do not identify an underlying cause for pneumonia
Esophageal obstruction*	Foreign body sometimes visible on thoracic radiographs Caution necessary with barium swallow procedures (barium aspiration risk)
Megaesophagus*	Often identifiable concurrently on thoracic radiographs
Other factors	
Bronchoesophageal fistula	Usually acquired via trauma (e.g., perforating esophageal foreign body)
Cleft palate	Congenital abnormality that may cause ingesta to enter nasal cavity with subsequent aspiration
Crowded or unclean housing	Persistence and concentration of infectious organisms in environment contributors to risk
Forceful bottle feeding*	Aspiration possible when care provider squeezes the nursing bottle during suckling, or if hole in nipple is too large
Gastric intubation*	—
Immune compromise	Specific conditions: anticancer or immunosuppressive chemotherapy; concurrent illness including feline leukemia, feline infectious peritonitis, diabetes mellitus, or hyperadrenocorticism; primary ciliary dyskinesia; immunoglobulin or leukocyte defects or deficiencies

Inadequate vaccination	Viral, bacterial, or parasitic infection with secondary opportunistic bacterial pneumonia
Induced vomiting*	—
Seizures*	Must differentiate pneumonia radiographically from noncardiogenic pulmonary edema
Tracheostomy*	—

Ancillary testing including a complete blood count (CBC), serum biochemistry profile, and urinalysis is important in all pneumonia suspects, but rarely contributes directly to the diagnosis. Although many animals with pneumonia have unremarkable CBC results, some of the most common CBC findings include leukocytosis characterized by neutrophilia, left shift, and monocytosis.[6] Animals that are severely affected may be leukopenic, and dogs with idiopathic eosinophilic pneumonia may have a peripheral eosinophilia. Nonspecific biochemical abnormalities may be present, most commonly hypoalbuminemia secondary to inflammation or vascular leak syndromes.

A coagulation profile often is helpful in assessing critically ill patients that may have a bleeding disorder or pulmonary hemorrhage. Additional testing for hypercoagulability (thromboelastography, D-dimer, fibrin degradation product, and antithrombin III levels) may be indicated in some patients, particularly if pulmonary thromboembolism is suspected.

Figure 22-1 **A,** Thoracic radiograph of a dog with pneumonia, dorsoventral projection. Alveolar infiltrates are seen most clearly in the central region of the right lung: the right middle lung lobe and adjacent regions of the right caudal lung lobe. **B,** Thoracic radiograph of the same dog, right lateral recumbent projection. The infiltrated lung is in the dependent region and not clearly visible; pneumonia could be falsely ruled out if this projection was the only one taken of this dog. Some gas is present in the esophagus *(asterisk)* and a prominent skin fold *(arrows)* should not be mistaken for a pleural fissure line. **C,** Thoracic radiograph of the same dog, left lateral recumbent projection. The infiltrates within the right middle lung lobe are clearly seen (note prominent air bronchograms), as is marked gaseous and soft tissue and fluid distention of the esophagus. Diagnosis: evidence of pneumonia and concurrent megaesophagus, suggesting aspiration as the inciting mechanism.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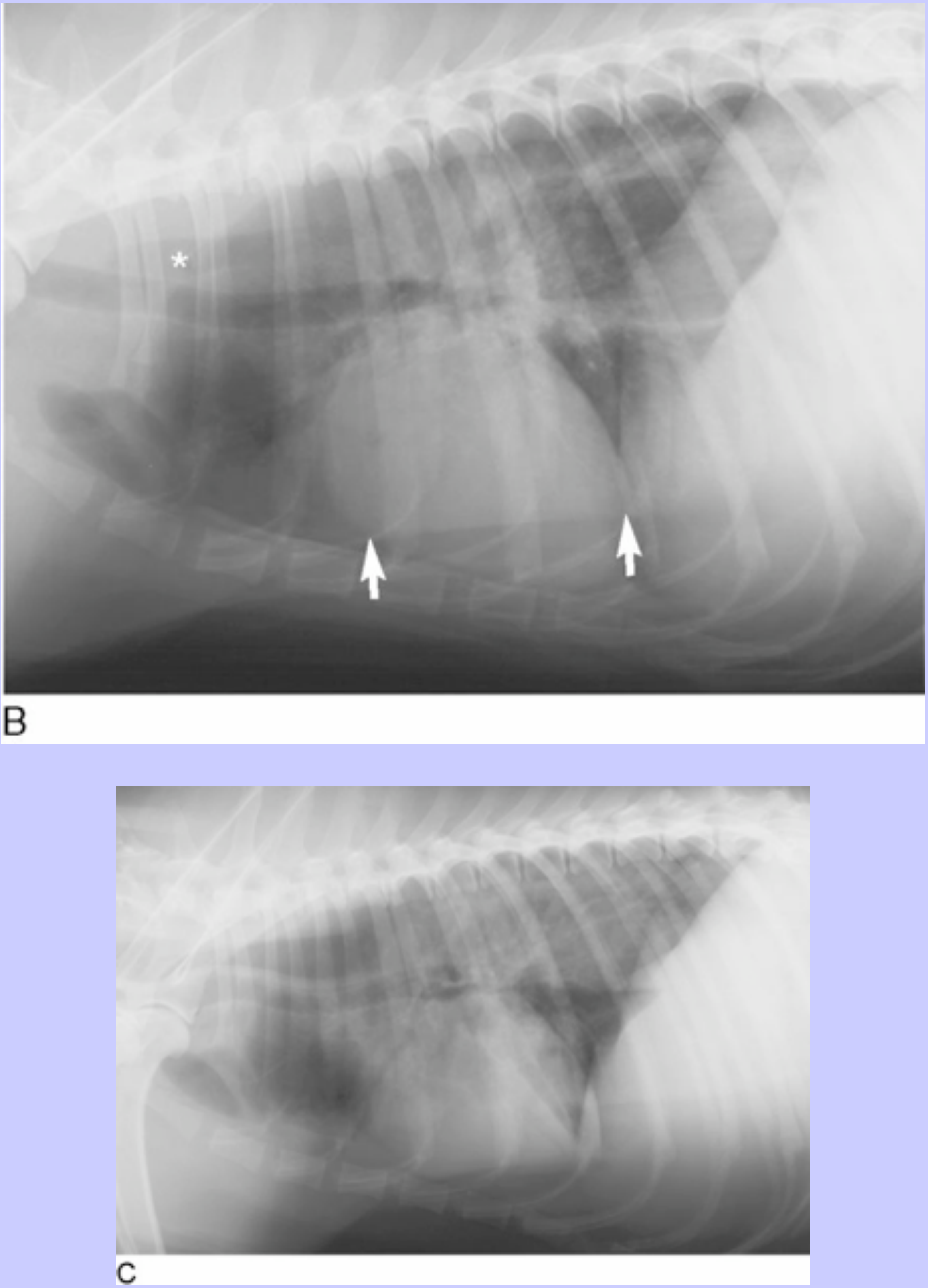
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Confirmation of bacterial lung infection requires demonstration of inflammation and infection in the lower respiratory tract. This information usually is obtained using transtracheal wash (TTW) or endotracheal wash (ETW), both of which can yield specimens for cytologic evaluation and bacterial or fungal culture and sensitivity. These tests are highly recommended when possible. In all cases, a complete evaluation first must be made to identify other conditions, such as pulmonary hemorrhage (typically caused by anticoagulant ingestion) or cardiogenic pulmonary edema, that would contraindicate such testing but could otherwise mimic pneumonia clinically.

Transcutaneous fine-needle aspiration of lung tissue in suspected cases of infectious pneumonia may be a low-yield, high-risk procedure, especially in dogs with diffuse pulmonary disease; a lower risk is expected if the patient is kept in lateral recumbency, aspirated side down, for 30 to 60 minutes post procedure (15 to 20 minutes if anesthetized).[9] In cats with unexplained pulmonary parenchymal disease, fine-needle aspiration may have better yield than from ETW.[7]

Additional diagnostic tests that may be indicated include fungal titers, serology for heartworm disease and toxoplasmosis, viral testing, and fecal examination (flotation, Baermann, and sedimentation) as dictated by each case.

Blood gas evaluation (and pulse oximetry) can be valuable in patients with pneumonia causing dyspnea or respiratory distress, especially at baseline and for subsequent monitoring.[1] An arterial blood sample is necessary for accurately measuring partial pressure of oxygen (PaO_2) and oxygen saturation (normal ≥80 mm Hg and ≥95%, respectively, when breathing room air at sea level). If hypoxemia is present, oxygen supplementation should be considered[1] (see Chapters 19 and 208, Oxygen Therapy and Blood Gas and Oximetry Monitoring, respectively). Abnormalities in dogs with pneumonia include hypoxemia, decreased oxygen saturation, and increased alveolar-arterial oxygen gradient. Typically, hypercapnia is not present.[8]

* Indicates predisposition to aspiration pneumonia.

22.5 PATHOPHYSIOLOGY

22.5.1 Mechanism

Infectious pneumonia represents an imbalance between natural defenses (upper airway mechanisms, airway barriers, humoral and cell-mediated immunity) and infectious agents. Pneumonia is characterized by bronchioalveolar inflammation. The bronchioalveolar junction is a major site of small particle (0.5 to 3 μm) deposition and is especially vulnerable to damage. Although large particles are cleared by the mucociliary apparatus, coughing, and the nasopharynx, particles smaller than 3 μm are deposited in the alveoli and bypass the upper respiratory tract defenses.[1] When large numbers of organisms or those with high virulence enter the lower airways, surfactant and alveolar macrophages are overwhelmed. An inflammatory response must ensue to effectively remove the offending organisms. Complex interactions between the cell-mediated and humoral immune systems, in conjunction with cytokines and chemokines, take place in an attempt to clear the offending agents.

Organisms and inflammatory exudates within the airways may lead to hypoxemia through several mechanisms. These include ventilation-perfusion mismatch, intrapulmonary shunting, and impaired diffusion. Severe or chronic pneumonia can lead to destruction of the alveolar walls, damage to type II pneumocytes, and increases in pulmonary vascular permeability, all of which contribute to acute lung injury and acute respiratory distress syndrome (see Chapter 24, Acute Lung Injury and Acute Respiratory Distress Syndrome). If the infection and inflammation are not restricted to the lungs, a systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction can occur (see Chapters 11 and 106, Systemic Inflammatory Response Syndrome and Sepsis, respectively). Animals with pneumonia may also develop bronchiectasis, pyothorax, polyarthritis, or glomerulonephritis secondary to antigen-antibody complex deposition.

22.5.2 Causes

Predisposing factors and disorders associated with pneumonia are listed in Table 22-1. Organisms commonly isolated via TTW from dogs with bacterial pneumonia include the gram-negative bacilli *Pasteurella* spp (22% to 28% of dogs with bacterial pneumonia) and Enterobacteriaceae such as *E. coli* (17% to 46%), and gram-positive cocci such as *Staphylococcus* spp (10% to 16%) and *Streptococcus* spp (14% to 21%).[4,5,8] Anaerobic bacteria are isolated in 10% to 21% of cases,[4,8] and their presence warrants suspicion for pulmonary abscess formation. *Mycoplasma* spp commonly are detected, either as sole organisms (8%) or as coinfections with other bacteria in a large proportion of dogs with bacterial pneumonia (62%).[5,9] Often, bacterial cultures from patients with pneumonia reveal multiple species of bacteria (e.g., 43%,[4] 47%,[8] and 74% [including *Mycoplasma*][5] of dogs and 38% of cats[3]). Fungal, viral, parasitic, and protozoal pneumonia may also occur secondary to predisposing factors as listed in Table 22-1.

22.6 TREATMENT

Animals that are breathing comfortably and have mild pneumonia as an incidental finding should be treated with appropriate long-term oral therapy and supportive care, including management of underlying or predisposing factors. Immunocompromised animals should be monitored frequently for worsening of clinical signs.

Oxygen supplementation should be provided to dyspneic and hypoxemic animals. Possible methods include flow-by delivery, intranasal cannula, oxygen cages, oxygen hoods, and oxygen tents, based on facilities and patient characteristics (see Chapter 19, Oxygen Therapy). The oxygen should be humidified and a sensor used for monitoring the inspired oxygen concentration. The approach to oxygen supplementation must be balanced against two important potential drawbacks: hyperthermia, especially for large breed or thick-coated dogs in an oxygen cage (even with air cooling settings) and reduced monitoring and handling due to the apparatus (oxygen cage, Elizabethan [E] collar). Intranasal oxygen should be delivered at a flow rate of 50 to 100 ml/kg/min. The lowest concentration of inspired oxygen that alleviates respiratory distress should be used. Long-term oxygen supplementation (>24 to 48 hours) should not exceed a concentration of 60% in order to reduce the risk of oxygen toxicity, which increases capillary permeability and denudes the alveolar epithelium.

Endotracheal intubation and positive-pressure ventilation (see Chapter 213, Basic Mechanical Ventilation) are indicated if severe dyspnea leads to impending respiratory fatigue, if severe hypoxemia (partial pressure of arterial oxygen [PaO_2] <60 mm Hg) is present, or if ventilatory failure (partial pressure of carbon dioxide ($PaCO_2$) >60 mm Hg) occurs. Fentanyl, pentobarbital, or propofol is typically chosen to immobilize a patient during ventilation (Table 22-2).

Empiric antibiotic therapy is often necessary initially, given the multiday turnaround time for bacterial culturing, yet misuse of antibacterial drugs may be detrimental. Samples that can be used for bacterial culture (ETW or TTW fluid, sputum, blood, urine) should be obtained as soon as possible. Antibiotic therapy should be initiated pending culture and sensitivity results (see Table 22-2). Empiric coverage should initially address gram-positive, gram-negative, and anaerobic bacteria. Animals with moderate to severe pneumonia should receive parenteral therapy.

For all these reasons, a common first choice approach is parenteral ampicillin and enrofloxacin, continued orally if bacterial culture results are positive and show susceptibility to these drugs. Preventive use of antibiotics (e.g., patient hit by a car, has pulmonary contusions; antibiotics given to prevent infection of contusions) is unsupported, helps to select resistant bacteria, confers an unjustified sense of therapeutic effect, and is not recommended. Overall, antibiotics that penetrate lung tissue are preferable (such as chloramphenicol, doxycycline, enrofloxacin, trimethoprim-sulfa, and clindamycin), although pulmonary inflammation may allow additional antibiotics to 94
penetrate during disease states. Long-term oral therapy (6 weeks to 6 months) may be necessary following 95
stabilization of the patient and marked improvement in oxygenating ability and radiographic infiltrates, but the exact duration depends on many elements, including underlying cause, local immunity, nature of pathogenic organisms, and client factors.

Table 22-2 Common Medications Used for Pneumonia

Drug	Effect or Spectrum	Dosage	Formulation
Antibacterial Agents: Injectable			
Amikacin (Amiglyde-V)	G–	15 mg/kg IV q24h provided renal function and hydration are sufficient	50 mg/ml
Ampicillin (many names)	G+, some G– (certain *E. coli* and *Klebsiella* strains), some anaerobes *(Clostridia)*	22 mg/kg IV q6-8h	1, 3, 6 mg vials
Cefoxitin (Mefoxin)	Some G+, some G–, some anaerobes	30 mg/kg IV q6-8h	1, 2, 10 g vials
Cephalothin, cefazolin (many)	G+	22 mg/kg IV q6-8h	1, 5, 10, 20 g vials
Enrofloxacin (Baytril)	G–, *Mycoplasma*	5 to 10 mg/kg, dilute 1:1 in saline and give IV q12h or 10 to 20 mg/kg IV q24h (dog) or as maximum 5 mg/kg q24h (cat)	22.7 mg/ml IV use is off-label
Gentamicin (Gentisin)	G–	6 to 8 mg/kg IV q24h provided hydration and renal function are sufficient	50 mg/ml
Metronidazole (Flagyl)	Anaerobes	10 to 15 mg/kg slow IV infusion q12h	500 mg/100 ml
Ticarcillin-clavulanate (Timentin)	G+, G–, anaerobes	40 to 50 mg/kg slow IV infusion q6h	3 g vial
Antibacterial Agents: Oral			
Azithromycin (Zithromax)	G+, G–, *Mycoplasma*	5 to 10 mg/kg IV or PO q24h	250, 600 mg tablets; 20 or 40 mg/ml oral solution
Clindamycin (Antirobe)	G+, *Mycoplasma, Toxoplasma,* anaerobes	5 to 10 mg/kg PO q8-12h	25, 75, 150 mg capsules; 25 mg/ml oral solution
Metronidazole (Flagyl)	Anaerobes	10 to 15 mg/kg PO q12h	250 mg tablets
Trimethoprim-sulfa (Ditrim, Tribrissen)	Some G+, some G–	15 mg/kg IV or PO q12h	30, 120, 480, 960 mg tablets
Sedatives and Anesthetics			
Fentanyl	For positive-pressure ventilation	5 µg/kg IV boluses to effect (maximum 50 µg/kg), then 5 to 7 µg/kg/hr IV (can add diazepam)	50 µg/ml (= 0.05 mg/ml)

Pentobarbital	For positive-pressure ventilation	2 mg/kg IV boluses to effect (up to 12 mg/kg) q4-6h or as needed to maintain sedation; 0.1 to 1 mg/kg/hr IV	50 mg/ml
Propofol (Diprivan, Rapinovet)	For positive-pressure ventilation	2 to 8 mg/mg IV bolus to effect, then 0.1 to 0.4 mg/kg/min IV	10 mg/ml
Diazepam	For use with anesthetics for positive-pressure ventilation	0.25 to 0.5 mg/kg IV, then 0.1 to 1.0 mg/kg/hr	5 mg/ml
Additional Therapeutic Agents			
Aminophylline	Bronchodilator and respiratory stimulant	5 mg/kg IV q8h (dilute and give over ≥30 minutes; up to 10 mg/kg in dog)	25 mg/ml
Caffeine	Bronchodilator, respiratory stimulant	5 to 10 mg/kg IV q6-8h (dilute and give over ≥30 minutes)	121 mg/ml
N-Acetylcysteine	Mucolytic	70 mg/kg IV q6h (dilute and give over ≥30 minutes)	20% solution
Terbutaline	Bronchodilator	0.01 mg/kg SC/IM/IV q4-6h	1 mg/ml

G+, Gram positive; *G−,* gram negative; *IM,* intramuscular; *IV,* intravenous; *PO,* per os; *SC,* subcutaneous.

Animals diagnosed with idiopathic eosinophilic pneumonia or sterile inflammatory pneumonia should be treated with glucocorticoids and removal of potential allergens.

The use of bronchodilators in animals with pneumonia is controversial, but may be helpful in select cases by 95
increasing airflow and mucokinetics via improving ciliary activity and increasing the serous nature of respiratory 96
secretions. However, their use may suppress the cough reflex, worsen ventilation-perfusion mismatch, and allow exudates within the affected lung to spread to unaffected portions of the lung. β_2-Agonists may also have a direct antiinflammatory effect by decreasing mucosal edema and downregulating cytokine release. Methylxanthine bronchodilators may also increase mucociliary transport speed, inhibit degranulation of mast cells, and decrease microvascular permeability and leak. Aminophylline is a respiratory stimulant that helps to increase the strength of diaphragmatic contractility to assist animals with ventilatory fatigue. Intravenous caffeine has been used in place of aminophylline, although its benefit in veterinary medicine remains unproven.

Mucolytic therapy is used commonly in veterinary patients, but scientific proof of its benefit is lacking. N-acetylcysteine (NAC) leads to a breakdown of the disulfide bonds in thick airway mucus and is also a precursor to glutathione, a free radical scavenger. Aerosolized NAC may irritate the airways and cause a reflex bronchoconstriction, so it is not recommended. Dilute intravenous NAC therapy has been used in small animals, but caution must be exercised.

Nebulization using 0.9% sodium chloride is an effective means of increasing particulate saline droplets in the inhaled air stream, to liquify thick lower airway secretions in order to hydrate the mucociliary system and enhance productive clearing. Vaporizers and humidifiers are not effective because the particle size generated with these methods is greater than 3 μm.

Coupage of the chest refers to a rapid series of sharp percussions of the patient's chest using cupped hands and closed fingers. Compression of air between the cupped hand and the chest wall creates vibrational energy that is transmitted to the underlying lungs to loosen deep secretions and consolidated areas of the lung and stimulate the cough reflex. Although its efficacy is contested in human medicine (see Chapter 23, Aspiration Pneumonitis and Pneumonia), coupage should be performed for several minutes over affected areas of the lung in small animal patients. Nebulization with or without coupage are performed every 4 to 6 hours. Coupage is unnecessary in animals that are coughing spontaneously and frequently, and may be contraindicated in animals that have a coagulopathy, have pain in the chest region, or are fractious.

Because atelectasis can exacerbate respiratory insufficiency, recumbent patients with pneumonia should be turned every 1 to 2 hours and supported in an upright position at least twice daily. Short walks should be encouraged as well.

22.7 ADDITIONAL MANAGEMENT CONSIDERATIONS

22.7.1 Contagion and Zoonosis

In most cases pneumonia-causing bacteria, as secondary invaders, are not contagious. However, contagion of the underlying process is possible by aerosol in dogs (canine distemper in the mucosal phase but not neurologic phase, infectious tracheobronchitis) and cats (feline herpesvirus, possibly calicivirus). Systemic mycoses are not contagious by aerosol from one animal to another. Zoonotic concerns are minimal if the human is not immunocompromised, although *Mycobacteria* spp in dogs and cats, and the agents of plague *(Yersinia pestis)* and tularemia *(Francisella tularensis)* in cats, have zoonotic potential for immunocompetent human hosts.

22.8 MONITORING

The cornerstones of monitoring are observation and diagnostic testing. The two must occur jointly, and in the busy critical care environment it is essential to avoid managing and monitoring the patient's results rather than the actual patient.

An attentive clinician can identify subtle changes in alertness, demeanor, appetite, respiratory effort, and other parameters that are not easily quantified but are highly valuable in identifying change, be it response to treatment or deterioration. More obvious changes in respiratory rate and effort, nasal flaring, cheek puffing, and orthopnea should be addressed immediately.

The interval between measurements of arterial blood gases and of pulse oximetry varies from hours to days, depending on initial severity and clinical progression. Serial pulse oximetry measurements performed every 1 to 6 hours may reveal overall trends in arterial oxygen saturation that forewarn of deterioration or improvement. However, single measurements should be interpreted with caution because erroneous readings may occur (see Chapter 208, Blood Gas and Oximetry Monitoring).

Thoracic radiographs may be used for monitoring progression of pulmonary disease, but for patients that are stable or improving, radiographic findings are unlikely to change during the first few days of treatment. Therefore retaking thoracic radiographs of a patient with pneumonia is not indicated during the first 3 to 5 days, except in a patient whose condition is deteriorating or in which unexpected new clinical signs emerge. It is normal for patients with severe pneumonia, especially puppies with *Bordetella* pneumonia, to look clinically and radiographically worse during the first few days of treatment.

22.9 PROGNOSIS AND OUTCOME

Antibiotic response is observed in most dogs (69% to 88%) when the pneumonia is managed appropriately.[5,6] Long-term outcome depends on the ability to resolve the inciting or associated cause, with cure expected when reversal of the trigger is possible (e.g., surgical foreign body removal) versus long-term management and frequent relapses expected when the predisposing cause lingers (e.g., idiopathic megaesophagus). Recurrent bouts of bacterial pneumonia should prompt the clinician to rule out bronchiectasis, an abscess or foreign body, structural changes, or inappropriate antibiotic therapy (e.g., discontinuing therapy prematurely or antibiotic resistance) that may allow a nidus of infection to persist within the lungs. Anecdotal reports and observations suggest that certain bacteria, certain underlying disorders, and empiric antibiotic treatment (instead of management based on culture and sensitivity) are associated with a worse prognosis.[5,6] Subjectively, initial severity of clinical signs and response during intensive treatment also offer prognostic information. However, a comprehensive assessment of specific, evidence-based prognostic parameters is lacking for small animal bacterial pneumonia. Fungal, viral, parasitic, and protozoal pneumonias vary in their response to management, often depending on pathogenicity of the offending organism, degree of systemic involvement, and underlying risk factors. 96 97

22.10 SUGGESTED FURTHER READING*

JC Angus, SS Jang, DC Hirsh: Microbiological study of transtracheal aspirates from dogs with suspected lower respiratory tract disease: 264 cases (1989–1995). *J Am Vet Med Assoc*. **210**, 1997, 55, *A retrospective, laboratory-based study of transtracheal aspirate specimens submitted to a university laboratory in northern California from dogs with clinical evidence of respiratory disease. Other than microbiologic information, clinical data are limited to signalment and predisposing or underlying condition. Much useful information on antibiotic sensitivity of bacteria*.

CA Brady: Bacterial pneumonia in dogs and cats. In LG King (Ed.): *Textbook of respiratory diseases in dogs and cats*. 2004, Saunders, Philadelphia, *Current, comprehensive overview of pneumonia (but not aspiration pneumonia, which is covered in the next chapter of the same book) in dogs and cats*.

OL Nelson, RK Sellon: Pulmonary parenchymal diseases. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2006, Saunders, St. Louis, *Comprehensive review of all major lung diseases of dogs and cats, with concise overview of pneumonia*.

WE Wingfield, VL Matteson, T Hackett, et al.: Arterial blood gases in dogs with bacterial pneumonia. *J Vet Emerg Crit Care*. **7**, 1997, 75, *Evaluation of arterial blood gas values assessed prior to treatment, and bacterial culture results obtained from transtracheal washes in 62 dogs with bacterial pneumonia*.

* See the CD-ROM for a complete list of references

23 Chapter 23 Aspiration Pneumonitis and Pneumonia

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23.1 KEY POINTS

- Aspiration pneumonitis has a biphasic pathogenesis. Initial events are caused by direct chemical injury. This is followed by localized inflammatory mediator cascades producing neutrophil chemotaxis, sequestration, and subsequent increased permeability edema.
- Aspiration pneumonia is an infectious process caused by either aspiration of contaminated material or by bacterial colonization of damaged lungs subsequent to a sterile aspiration episode. Acid-induced lung injury enhances bacterial adherence to and reduces bacterial clearance from the lungs.
- Diagnosis is typically based on history, physical examination, and radiography. The severity of respiratory compromise is best monitored by arterial blood gas analysis.
- Management is principally supportive, consisting of airway management, cardiovascular support, oxygen therapy, and respiratory physiotherapy.
- Antimicrobial drug therapy should be directed by cytologic testing, Gram stain, and bacterial culture and sensitivity on samples collected by tracheal wash (TW) or bronchoalveolar lavage (BAL).
- The incidence of aspiration pneumonia can be reduced by recognizing the risk factors and attempting to control or minimize them.

23.2 INTRODUCTION

Aspiration pneumonitis and pneumonia frequently coexist in veterinary patients and may cause significant morbidity and mortality. The pathophysiology of both conditions shares some common features, namely the initiation of a localized inflammatory cascade with resultant impairment of respiratory function. Both conditions may incite development of acute respiratory distress syndrome (ARDS) or the systemic inflammatory response syndrome (SIRS).[1] A number of risk factors exist for aspiration of gastric contents (Box 23-1). Emergency clinicians should be aware of these risk factors and have an understanding of the subsequent pathogenesis of pulmonary damage to aid in prevention and early recognition in order to enable optimal patient monitoring and treatment.

23.3 ASPIRATION PNEUMONITIS

23.3.1 Etiology

Aspiration pneumonitis is defined as acute lung injury due to inhalation of chemical irritants such as acidic stomach contents, hydrocarbons, or water (saltwater or fresh water near-drowning). The most common cause of aspiration pneumonitis is inhalation of gastric contents, and this will be the focus of the ensuing discussion.

Inhalation of small quantities of oropharyngeal material contaminated by bacteria likely occurs in normal animals, but bacterial colonization of the airway mucosa is prevented by rapid removal of this material by mucociliary clearance. In human patients with decreased levels of consciousness secondary to head trauma, seizures, sedation, or anesthesia the incidence of aspiration is greatly increased.[2] A landmark study in 1946 reported acute respiratory failure in 66 women due to aspiration of stomach contents during anesthesia for obstetric procedures and suggested causal mechanisms for the associated pulmonary injury.[3] The study also investigated the effects of a variety of solutions on the lungs of rabbits and concluded that aspirate acidity was the key factor in determining the severity of injury.

23.3.1.1

Box 23-1 Disorders and Conditions Predisposing to Aspiration of Gastric Contents

23.3.1.1.1

Large Volumes of Intragastric Food or Fluid

Delayed gastric emptying

Gastric outflow obstruction

Pain medication or opioid administration

Gastrointestinal motility disorders

Ileus

Pregnancy

Obesity

Recent meal

Overfeeding by the enteral route

23.3.1.1.2

Esophageal Disorders

Esophageal obstruction

Esophageal dysmotility

Megaesophagus

Myasthenia gravis

Esophageal reflux

Lower esophageal sphincter impairment

Drug administration

Nasogastric tube placement

23.3.1.1.3 Impaired Consciousness

Sedation, general anesthesia

Head trauma

Seizures

Encephalopathy

Coma

23.3.1.1.4 Impaired Airway Function

Laryngeal or pharyngeal dysfunction or surgery

Airway trauma

23.3.1.1.5 Other

Tracheostomy

Gastric intubation

Cleft palate

Weakness, paresis, paralysis

Factors affecting severity have since been further described. The magnitude of lung injury depends on the pH, volume, osmolality, and presence of nonsterile particulate matter in the aspirate.[4,5] Severe histologic damage is caused by aspirates more acidic than pH 1.5, but little or no damage is caused by those with pH greater than 2.4.[6] Particulate matter causes pulmonary injury by airway obstruction, prolongation of the inflammatory response, and by acting as a source of and nidus for bacterial infection.[6,7] Aspiration of gastric contents containing particulate matter may cause severe pulmonary injury even if the pH is above 2.5.[8,9]

23.4 ASPIRATION PNEUMONIA

23.4.1 Etiology

Aspiration pneumonia refers to a pulmonary bacterial infection that develops following aspiration, but the distinction between pneumonitis and pneumonia is poorly defined in veterinary species. Aspiration pneumonia can result from bacterial colonization of lungs injured by acid aspiration or from aspiration of contaminated material. Because oropharyngeal colonization with pathogenic bacteria such as *Pasteurella* spp is extremely common in dogs and cats, both mechanisms likely occur. Aspiration of saltwater, oils, and liquid hydrocarbons may be included in the definition of aspiration pneumonia even though concurrent bacterial infection may not be present.

23.5 ASPIRATION PNEUMONITIS AND PNEUMONIA

23.5.1 Pathophysiology

The accepted biphasic model for acute lung injury following acid aspiration was developed following murine experiments in which lung permeability changes following direct tracheal instillation of hydrochloric acid were evaluated and the chronology of the histologic changes described.[10]

The first phase of lung injury, which begins immediately following aspiration, results from direct effects of the acidic aspirate. This is initially a chemical burn that damages the bronchial and alveolar epithelium and the pulmonary capillary endothelium.[11] Pulmonary capillary permeability increases following acid stimulation of sensory neurons in the tracheobronchial smooth muscle. These sensory (substance P–immunoreactive) nerves are involved in the control of bronchial smooth muscle tone and vascular permeability. Stimulation of these nerves induces release of multiple tachykinin neuropeptides such as substance P and neurokinin A.[12] Neurogenic inflammation, bronchoconstriction, bronchial mucus secretion, cough, vasodilation, and increased vascular permeability result. Permeability changes are maximal 1 to 2 hours after aspiration. Histologically, first phase damage consists of epithelial and endothelial degeneration, necrosis of type I alveolar cells, and intraalveolar hemorrhage.

The second phase of acid-induced lung injury starts 4 to 6 hours after aspiration and may continue for up to 2 days. It is characterized by additional, larger increases in pulmonary capillary permeability and protein extravasation than during the first phase, leading to extensive pulmonary edema formation, further compromising gas exchange and depleting intravascular volume.[10] Neutrophils initially are attracted to the lungs by chemotactic mediators such as interleukin-8, tumor necrosis factor-α, and macrophage inflammatory protein-2 released by alveolar macrophages following the initial aspiration episode.[13-15] The second phase involves the generation of a localized proinflammatory state by activation of sequestered neutrophils. Interleukin-8 is the main stimulus for neutrophil chemotaxis and also upregulates neutrophil β_2-integrin endothelium receptors, mediates transendothelial neutrophil migration, and primes neutrophils for activation.[13] Combination acid-particulate aspirates induce larger and longer lasting tumor necrosis factor-α expression than aspiration of acid alone.[16] Neutrophils damage tissue by production and release of oxygen free radicals and proteolytic enzymes. High levels of serine proteases released by the sequestered, activated neutrophils seem to play a more important role in causing tissue damage than leukocyte-derived reactive oxygen species.[17]

The contralateral lung may be affected even if aspiration is unilateral. Complement activation resulting from mast cell degranulation stimulated by tachykinins mediates this response.[18,19] In guinea pig models, tachykinin 98 release in the lungs occurs following esophageal stimulation by gastric acid due to the presence of 99 nonadrenergic, noncholinergic neural networks between the esophagus and the trachea.[20]

Aspiration pneumonia may develop concomitantly with pneumonitis if the aspirated contents are contaminated with oropharyngeal bacteria. Alternatively, aspiration pneumonia may develop from pneumonitis by subsequent bacterial colonization of the respiratory tract. Likely bacteria include commensals such as *Staphylococcus* spp, coliforms such as *E. coli* and *Klebsiella* spp, oropharyngeal *Mycoplasma* spp, and primary respiratory pathogens including *Pasteurella* spp, *Pseudomonas* spp, *Bordetella* spp, and *Streptococcus* spp.[21-24] Gastric acid aspiration enhances bacterial adherence to the respiratory epithelium and reduces pulmonary clearance of bacteria. Acid injury may also facilitate bacterial adherence by upregulating expression of certain receptors providing de novo binding sites or by damaging epithelial cells, allowing respiratory pathogens to bind preferentially.[25] Bacterial adherence may be mediated by pili, which access the cell surface following acid injury.[26,27]

Ultimately, the vascular permeability changes lead to pulmonary edema formation, focal atelectasis, and collapse of alveoli, resulting in hypoventilation and shunting. The inflammatory response to bacterial infection exacerbates this and hypoxia may develop as a consequence of ventilation-perfusion (V/Q) mismatch and reduced lung compliance.

23.5.2 Diagnosis

23.5.2.1 History

A full clinical history from the primary caregiver is essential in making a diagnosis of aspiration pneumonia. Aspiration episodes may be witnessed, but frequently go unnoticed and unreported. Hospitalized patients perceived as at risk (see Box 23-1) should be monitored closely and suspicion of aspiration aroused if respiratory distress develops acutely.

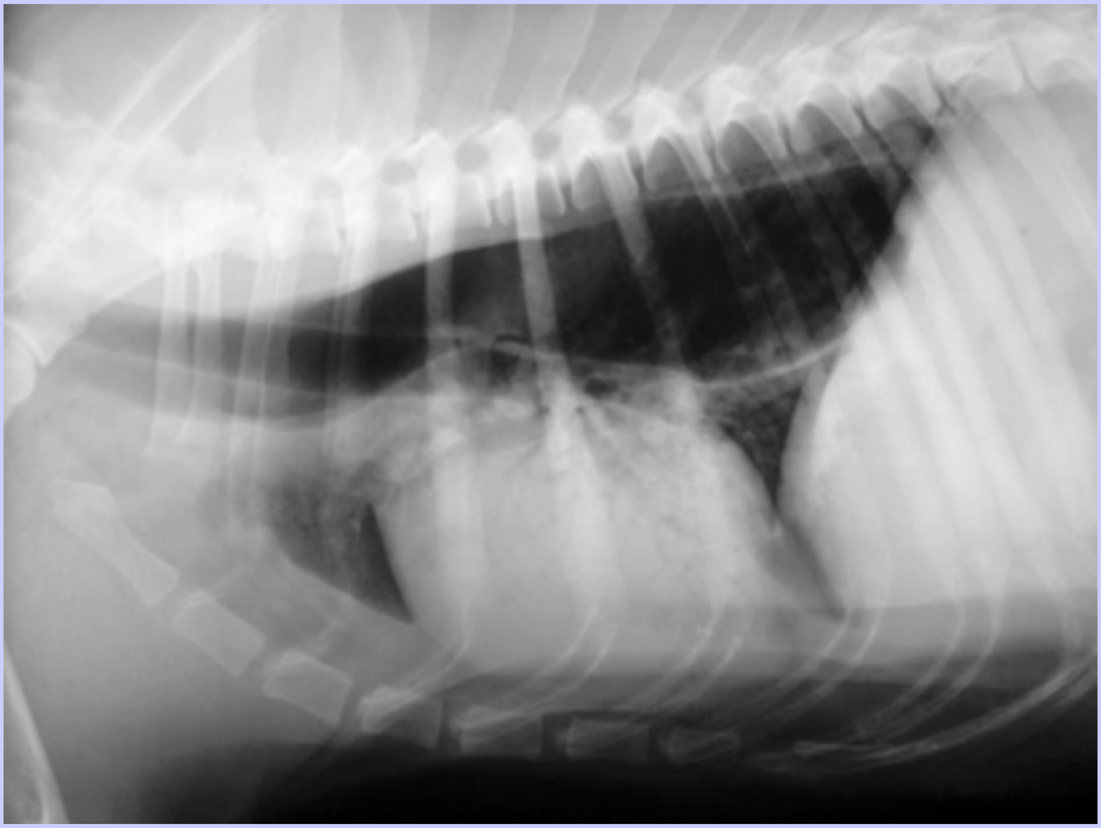
23.5.2.2 Physical Examination

The clinical signs of aspiration pneumonia and pneumonitis include acute-onset respiratory distress, potentially accompanied by cyanosis, cough, collapse, pyrexia, or a mucopurulent nasal discharge. Respiratory pattern, rate, rhythm, effort, and depth should be observed. Patients with aspiration pneumonia frequently have abnormal lung sounds unless auscultated soon after a small-volume aspiration. It is important to consider whether the sounds heard are appropriate for the patient's respiratory rate and effort. Lung sounds in patients with aspiration pneumonia are often louder than normal. Fine crackles may be heard during inspiration, especially in the cranioventral areas. Rarely, lung sounds may be significantly decreased if a large bronchus becomes filled with exudates and cellular debris such that air can no longer pass through. Auscultation of the lung fields, subdivided into smaller areas, can aid in lesion localization and improve detection rates (Color Plate 23-1). Thoracic percussion is occasionally used to determine the relative densities of portions of the lung fields. Areas of decreased sound are suggestive of lung lobe consolidation.

23.5.2.3 Radiography

Thoracic radiography is the mainstay for the diagnosis of aspiration pneumonia. Patients typically develop an alveolar lung pattern as a result of displacement of air from alveoli by fluid accumulation and cellular infiltration. In the dog and cat, aspiration pneumonia typically affects the right middle lung lobe and ventral parts of the other lobes (Figure 23-1). Lesion distribution may be affected by patient position at the time of aspiration. History, clinical suspicion, and radiographic lesions are often sufficient to diagnose aspiration pneumonia. Other radiologic differential diagnoses include infectious bronchopneumonia, pulmonary hemorrhage, neoplasia, and lobar collapse or torsion. Radiographic signs of aspiration pneumonia may change markedly over time, typically lag hours behind the onset of respiratory distress, and may persist for several days despite clinical improvement. In humans the degree of alveolar infiltration visible radiographically correlates poorly with arterial hypoxemia, degree of dyspnea, or prognosis.

Figure 23-1 A right lateral thoracic radiograph of a dog with aspiration pneumonia secondary to megaesophagus. There is an alveolar pattern in the area of the right middle lung lobe and overlying the cardiac silhouette. Several air bronchograms can be seen.



Radiography may be useful in assessing factors that predispose to aspiration pneumonia. Megaesophagus may be identified on plain thoracic radiographs. Contrast studies may be necessary to investigate and identify pharyngeal or esophageal motility disorders. However, contrast media may be aspirated by these patients (Figure 23-2), so it should be used with caution, especially in patients with megaesophagus.

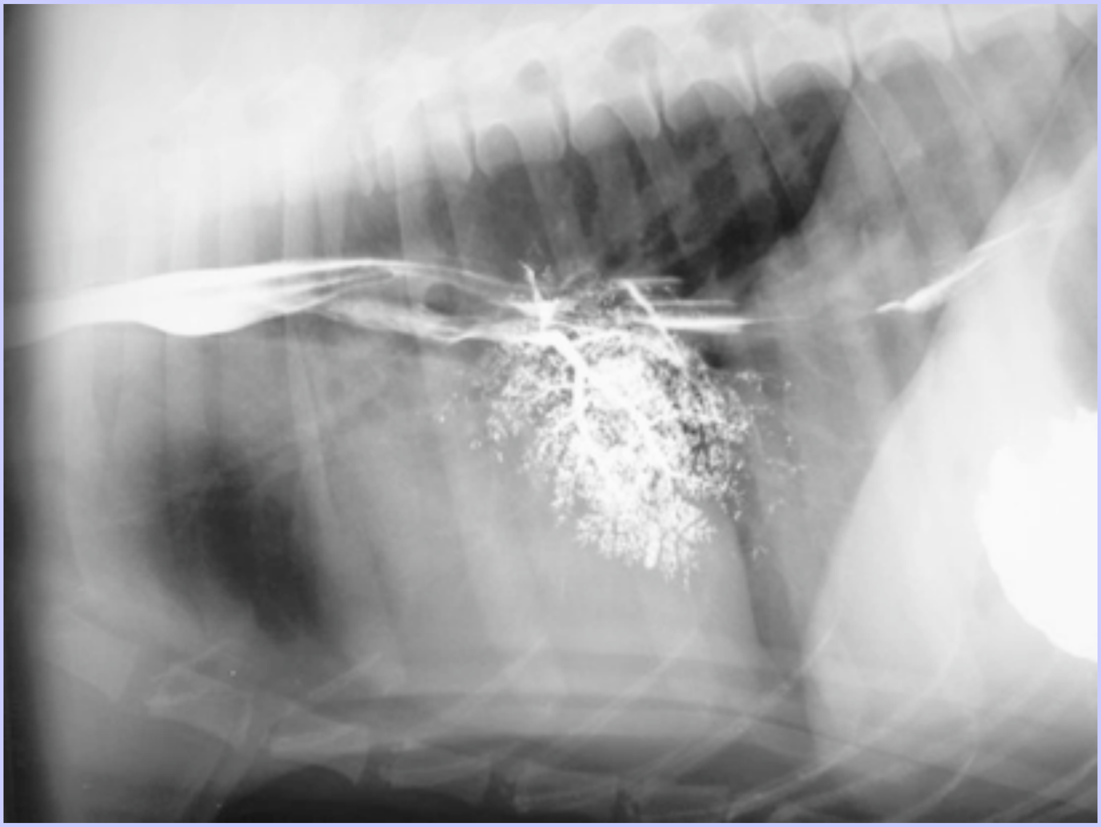
23.5.2.4 Tracheal Wash

Tracheal wash (TW) is a minimally invasive diagnostic test used in both dogs and cats to obtain airway samples for cytologic analysis and bacterial culture. TW can be performed by the transtracheal (TTW) or endotracheal (ETW) routes, depending on the size and stability of the patient. Both techniques are suitable for investigation of suspected aspiration pneumonia. One experimental study in dogs with *Streptococcus pneumoniae* infection found that TTW was as sensitive as transbronchial biopsy, lung aspirates, and bronchoalveolar lavage (BAL).[28] TTW had poorer specificity, however, and produced fewer pure cultures than did other techniques. Sensitivities of between 45% and 57% have been reported for diagnosis of bacterial pneumonia by TTW.[22,29,30]

23.5.2.5 Bronchoscopy and Bronchoalveolar Lavage

Bronchoscopy allows visualization of the luminal surface of the respiratory tract typically to the tertiary bronchi level, assessment of airway injury, and collection of lavage samples. The procedure is not without risk in patients suffering from aspiration pneumonia that have respiratory compromise, hypoxemia, or hypercapnia. BAL performed at the time of bronchoscopy is a more invasive diagnostic sampling technique than TW. BAL may cause transient but potentially significant decreases in lung function that may not be well tolerated in patients with preexisting compromise. BAL retrieves larger volumes of fluid directly from visibly affected areas than TW, potentially providing greater sensitivity, specificity, and increased diagnostic yield. Compared with TW, BAL may have superior diagnostic yield for investigation of lower airway, alveolar, and interstitial disease.

Figure 23-2 A right lateral thoracic radiograph of a dog with an esophageal motility disorder, showing contrast material within the esophagus, trachea, and the right middle lung lobe.



23.5.2.6 Complete Blood Count and Serum Biochemistry

Blood samples for complete blood count (CBC) and serum biochemistry values are indicated in all patients suspected of having aspirated gastric contents. Common hematologic abnormalities include a neutrophilia or neutropenia with a left shift and lymphopenia. Although these changes are nonspecific, they may reflect the degree of inflammatory response. These CBC changes may take up to 24 hours to develop following an aspiration event. Both CBC and serum biochemistry analysis are useful in identifying and investigating comorbidities.

23.5.2.7 Arterial Blood Gas Analysis

Changes in arterial blood gas values have minimal lag time following aspiration. They provide an objective assessment of respiratory functional impairment, which can be measured serially to chart the course of the disorder as well as to guide and monitor therapeutic interventions. Typical changes include hypoxemia and hypocapnia, although patients may become hypercapnic when the respiratory muscles become fatigued or severe pulmonary parenchymal disease is present.

23.5.3 Treatment

23.5.3.1 Airway Management

Following a witnessed aspiration event, airway patency should be established. Endotracheal intubation may be necessary, and solid foreign material obstructing the airway should be removed immediately. Aspirated liquid material will disperse quickly, but suctioning of the pharynx may reduce further fluid entering the trachea and may be necessary to allow intubation. Suctioning of the airway may not always be successful in removing fluid; however, it may stimulate coughing, which is protective. Although therapeutic bronchoscopy for lavage of the affected areas has been suggested, it is of unproven benefit in veterinary patients and, given the pathogenesis of acid-induced lung injury and the risks of anesthesia, is not routinely recommended.

23.5.3.2 Oxygen Therapy

Aspiration typically results in severe hypoxemia due to V/Q mismatch, intrapulmonary shunting, and hypoventilation. Oxygen therapy is indicated in cases of aspiration pneumonia that exhibit hypoxemia or inadequate hemoglobin saturation documented by arterial blood gas analysis or pulse oximetry. Numerous minimally invasive techniques are described, including nasal flow-by, masks, insufflation via nasopharyngeal catheters, oxygen hoods, and oxygen cages (see Chapter 19, Oxygen Therapy). Oxygen administration should be sufficient to alleviate respiratory distress and ensure adequate arterial partial pressure of oxygen (PaO_2). Oxygen toxicity has not been reported in the clinical veterinary literature but experimental studies suggest prolonged high inspired oxygen concentrations may have detrimental effects, including increased lung permeability, protein extravasation, and impaired compliance. Oversupplementation should be avoided.[31,32]

23.5.3.3 Mechanical Ventilation

Ventilatory support may be required in patients with progressive ventilatory failure (hypercarbia) or failure of pulmonary oxygen delivery or exchange (hypoxemia) where less invasive methods of oxygen support are unsuccessful (see Chapter 213, Basic Mechanical Ventilation). The decision to put an animal on mechanical ventilation typically is made on the basis of serial arterial blood gas analyses and repeated patient examinations. Patients with aspiration pneumonia generally are considered to have a poor prognosis if mechanical ventilation is required, although ventilation may be lifesaving. Patients with pulmonary parenchymal disease causing severe hypoxemia have a much higher risk of alveolar rupture and pneumothorax, capillary endothelial damage, impairment of venous return, and ventilator-associated pneumonia, compared with patients with hypercapnia and ventilatory failure.[33]

23.5.3.4 Bronchodilators

Drugs such as salbutamol, terbutaline, and aminophylline may be useful in acute aspiration pneumonitis, because bronchoconstriction is part of the physiologic response to acid injury. The use of bronchodilators in animals with pneumonia is controversial, but they may be helpful in select cases by increasing airflow and mucokinetics via improving ciliary activity and increasing the serous nature of respiratory secretions. Their use may suppress the cough reflex, worsen V/Q mismatch, and allow exudates within the affected lung to spread to unaffected portions of the lung. Aminophylline may also act by decreasing inflammation and reducing the oxygen demands of breathing (see Chapter 22, Pneumonia).

23.5.3.5 Cardiovascular Support

Fluid therapy should be used judiciously in patients with aspiration pneumonitis or pneumonia, because any increase in pulmonary capillary hydrostatic pressure will tend to exacerbate fluid extravasation into the alveoli. The patient's intravascular volume and hydration status should be assessed frequently and fluid therapy tailored to individual patient requirements, with due consideration for the degree of cardiovascular and respiratory compromise.

23.5.3.6 Nebulization and Coupage

Nebulization and coupage are a form of respiratory physiotherapy that aims to humidify bronchial secretions and encourage their removal from the airways. Two human clinical studies evaluating physiotherapy in patients with bacterial pneumonia concluded that chest physiotherapy did not reduce duration of hospital stay or improve lung function.[34,35] In the second study, patients with pneumonia who received chest physiotherapy had a longer duration of pyrexia than those not receiving treatment.[35] There have been no studies of respiratory physiotherapy in veterinary patients (see Chapter 22, Pneumonia).

23.5.3.7 Antibiotics

Antimicrobial therapy is not indicated in the early stages of aspiration pneumonitis. Antibiotics are appropriate for aspiration pneumonia, and selection should be based on culture and sensitivity results from samples obtained by TW or BAL. This will not be possible in all cases and results will not be immediately available. Cytologic analysis of airway washes, including Gram stain, can be used to guide antimicrobial choices while culture results are pending. In general, broad spectrum antimicrobial agents should be chosen with consideration of local resistance profiles. Anaerobic coverage is unlikely to be necessary.[36] Antimicrobial therapy should be reevaluated frequently on the basis of clinical response and culture results. The pharmacokinetics of antimicrobial agents should also be considered. Polar drugs such as the cephalosporins and penicillins penetrate poorly, although they may achieve higher levels in inflamed tissues. Lipophilic molecules such as the fluoroquinolones penetrate natural body barriers readily and will reach therapeutic levels in bronchial secretions (see Chapter 22, Pneumonia).

23.5.3.8 Glucocorticoids

Glucocorticoids could theoretically be beneficial in suppressing the proinflammatory state that occurs in aspiration pneumonitis. However, these agents suppress the immune system by decreasing levels of T-lymphocytes, inhibiting leukocyte chemotaxis and phagocytosis and antagonizing complement. They also increase the risk for gastrointestinal ulceration. Thus glucocorticoids likely negate the protective immune response to acid aspiration and may increase the risk of bacterial pneumonia.[37] Their use is not recommended.

23.5.4 Prevention

Arguably, the best method for managing aspiration pneumonia is to prevent its occurrence. This will not be possible in all patients, especially those with pathologic impairment of their protective airway reflexes or with diseases that predispose them to vomiting or regurgitation. When medical or surgical interventions place patients at risk, techniques should be employed to minimize the risk, including fasting and the use of prokinetic agents, antiemetic medications, and gastric alkalinization.

Evacuation of the stomach using a nasogastric tube or via suction in anesthetized patients may decrease the frequency and volume of vomitus. Fasting for 6 hours prior to anesthesia is common practice to minimize residual gastric volume. In humans this consistently reduces the amount of food in the stomach, but the effect on gastric pH is variable.[38] In dogs, fasting reliably increases gastric pH to a median 24-hour intragastric pH of 4.4.[39] Gastric alkalinization to a pH higher than 2.5 may be appropriate to minimize the risk of acid-induced lung injury in patients considered to be at risk for aspiration. Famotidine, pantoprazole, or omeprazole, but not ranitidine, would be suitable to achieve this in canine patients that have not fasted.[39]

There is some evidence in human medicine suggesting that gastric alkalinization promotes bacterial colonization within the stomach and thus increases the potential for aspiration pneumonia. This subject is still a matter of controversy. Several recent human studies found no increase in the rate of ventilator-associated pneumonia in patients receiving gastroprotective drugs, suggesting that any increased risk is minimal and is independent of the drug used.[40,41] Unfortunately, similar studies in the veterinary field are not available, thus firm recommendations cannot be made (see Chapter 181, Gastrointestinal Protectants).

Prokinetic drugs such as metoclopramide enhance gastric emptying by increasing gastric contraction and small intestinal peristalsis. Metoclopramide is also an antidopaminergic antiemetic which, in combination with a histamine-2 (H_2) receptor antagonist given 12 hours before and on the day of anesthesia, reliably reduces the risk of aspiration in humans. The intravenous administration of metoclopramide and an H_2 receptor antagonist may be useful for emergency anesthesia in veterinary patients that have not been fasted.

Enteral feeding, whether it is esophageal, gastric, or postpyloric, predisposes patients to aspiration pneumonia.[42,43] Bacterial colonization of enteral feeding tubes occurs within 4 days of intensive care unit admission in human patients receiving gastric alkalinizing drugs.[44] Systemic antibiotics will neither prevent nor manage this colonization. Because nutritional support of critical patients is important for recovery, the aspiration risk should be minimized using safe feeding protocols. Patients should not be fed enterally while recumbent, and the residual gastric volume should be ascertained prior to administration of food. Feeding should be stopped at any sign of patient discomfort or resistance and the tube position checked.

23.6 SUGGESTED FURTHER READING*

JC Angus, SS Jang, DC Hirsch: Microbiological study of transtracheal aspirates from dogs with suspected lower respiratory tract disease: 264 cases (1989-1995). *J Am Vet Med Assoc*. **210**, 1997, 55, *A retrospective case series from the University of California, Davis, which set out to document the most commonly isolated bacteria associated with lower respiratory tract disease in dogs*.

SK Kallar, LL Everett: Potential risks and preventative measures for pulmonary aspiration: new concepts in preoperative fasting guidelines. *Anesth Analg*. **77**, 1993, 171, *A review of the literature and proposal of guidelines for preoperative fasting to reduce the risk of aspiration of gastric contents during the perioperative period*.

TP Kennedy, KJ Johnson, RG Kunkel, et al.: Acute acid aspiration lung injury in the rat: biphasic pathogenesis. *Anesth Analg*. **69**, 1989, 87, *An important study that first delineated the biphasic pathogenesis of the response to acid aspiration. Pulmonary permeability changes were measured with a radiolabeling study in a murine model*.

PE Marik: Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med*. **344**, 2001, 665, *An excellent review of the topic in human medicine by a leading human critical care clinician*.

KM Moser, K Maurer, L Jassy, et al.: Sensitivity, specificity, and risk of diagnostic procedures in a canine model of *Streptococcus pneumoniae* pneumonia. *Am Rev Respir Dis*. **125**, 1982, 436, *An experimental study investigating various methods for the diagnosis of bacterial pneumonia, including transtracheal aspiration, transthoracic needle aspiration, catheter brush biopsy, and transbronchial biopsy*.

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* See the CD-ROM for a complete list of references.

24 Chapter 24 Acute Lung Injury and Acute Respiratory Distress Syndrome

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24.1 KEY POINTS

- Acute lung injury (ALI) is a severe complication of critical illness or injury. Acute respiratory distress syndrome (ARDS) is a more severe form of ALI.
- Inflammation and alterations in the alveolar-capillary membrane lead to the influx of inflammatory cells and proteinaceous fluid, causing alveolar flooding and resulting in severe hypoxemia.
- ALI and ARDS are clinical diagnoses.
- The relative clinical importance of ALI in animals is likely growing, but uncertain.

24.2 INTRODUCTION

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) represent life-threatening complications of critical illness in people. These complications reflect the advances in critical care that have occurred in human medicine during the last 40 years. As a result of these advances most patients now survive beyond the initial injury and illness, but they are at risk of developing complications such as multiple organ failure, ALI, and ARDS.

Early pathologic and clinical reports from World War I describe findings consistent with the modern definitions of ALI, although it was not recognized as a clinical entity.[1] During the 1960s it was recognized that although previously healthy, young soldiers injured in combat could be resuscitated in the field, they would often die days to weeks later from progressive multiple organ failure. Ashbaugh and colleagues are credited with the first modern description of adult respiratory distress syndrome in 1967.[2] Since its recognition, ARDS has remained a devastating complication of critical illness, with survival rates now only slightly better than they were 40 years ago. Adult respiratory distress syndrome was reclassified as acute respiratory distress syndrome in 1994 to include pediatric patients.[3]

24.3 HUMAN PERSPECTIVE

Acute lung injury–acute respiratory distress syndrome (ALI-ARDS) has been defined by the American-European Consensus Conference of 1994 as severe respiratory failure following a catastrophic event.[3] The catastrophic event may be pulmonary (e.g., aspiration pneumonia or pulmonary contusion) or extrapulmonary (e.g., abdominal sepsis).

More recently, other inciting events have been recognized to result in a specific form of ALI. For example blood transfusions can be associated with pulmonary injury, a syndrome that is termed *transfusion-related acute lung injury (TRALI)*. ALI-ARDS is further defined by a low oxygenation index (PaO_2-to-FiO_2 ratio). Patients with ALI have an oxygenation index of less than 300, and those with the more severe category of ARDS have an index of less than 200.[3] Additional diagnostic criteria include bilateral pulmonary infiltrates on thoracic radiographs, exclusion of cardiogenic pulmonary edema, and decreased lung compliance.

The most consistent histologic pattern appreciated with ARDS is diffuse alveolar damage.[4,5] However, this pattern is considered rather nonspecific and may be associated with a variety of clinical syndromes in addition to ARDS, including other pulmonary conditions such as acute interstitial pneumonia, inhalation of toxic substances, or prior treatment with amiodarone.[6-8]

In cases of suspected ARDS, stages of lung injury include exudative, proliferative, and, ultimately, fibrotic phases. During the initial insult, hemorrhage and protein-rich pulmonary edema accumulate in the alveoli. The initial exudative phase (days 0 to 6) is characterized by protein-rich edema, the influx of neutrophils, and eosinophilic hyaline membranes in the walls of the alveolar ducts. This is followed by the proliferative phase (days 4 to 10) characterized by a decrease in edema and hyaline membranes and an increase in interstitial fibrosis. The final fibrotic phase (day 8 onward) is characterized by pronounced fibrosis that ultimately may obliterate areas of the lung. Histopathologic criteria are useful in understanding the pathophysiology and evaluating patients with ARDS, although this syndrome should be considered a clinical diagnosis; a lung biopsy or autopsy is not required for diagnosis.

The arterial hypoxemia observed in ALI-ARDS develops from a variety of factors including ventilation-perfusion (V/Q) mismatch, shunting of venous blood into the arterial circulation, and low alveolar partial pressure of oxygen (P_AO_2). Diffusion limitation is rarely a major contributor to hypoxemia in people with ARDS. V/Q mismatch is the most clinically relevant cause of hypoxemia in people with ARDS. Regions with low V/Q are a result of partial alveolar collapse or obstruction caused by factors such as accumulation of exudate and loss of surfactant. When complete alveolar collapse or obstruction occurs it creates a physiologic shunt.

Physiologic shunt will permit deoxygenated venous blood to flow directly into the arterial circulation without exposure to functional gas exchange units. The result is a reduction in the arterial partial pressure of oxygen (PaO_2). This cause of hypoxemia is not responsive to oxygen therapy; mechanical ventilation may allow recruitment of previously collapsed alveoli, reducing the degree of physiologic shunt. Importantly, venous oxygen desaturation will magnify abnormalities associated with shunting, and efforts to improve venous oxygenation by improving perfusion and decreasing oxygen consumption will improve arterial oxygenation in those with a significant physiologic shunt.

Decreased P_AO_2 may be caused by hypoventilation associated with low pulmonary compliance. This type of hypoxemia generally improves with supplemental oxygen.

In people with ALI-ARDS, pulmonary functional abnormalities noted in addition to hypoxemia include decreased functional residual capacity, mild to moderate reductions in the forced expiratory volume in 1 second and forced vital capacity, decreased diffusing capacity, decreased compliance, and increased resistance. Alterations in surfactant production and composition may also contribute to alveolar collapse, and pulmonary arterial hypertension may result from increased pulmonary vascular resistance. Limited pulmonary function testing has been performed in veterinary patients with ALI-ARDS.

The underlying cause for ALI and ARDS is often unknown. These syndromes should be considered the final end points of a variety of pathophysiologic insults that can be infectious, traumatic, inflammatory, or immune mediated in origin. Common features of massive injury include pronounced microvascular permeability, leukocyte activation, and alterations in cytokine production. Inflammatory mediators are responsible at least in part for the development and propagation of ALI-ARDS. Overzealous response on the part of the host may magnify the initially appropriate inflammatory response and result in perpetuation of injury. Major humoral mediators of ALI-ARDS include the proinflammatory cytokines interleukin-1 and tumor necrosis factor-α, and cellular mediators include neutrophils and macrophages.

Therapy for ALI-ARDS is primarily supportive, and no specific pharmacologic therapy is associated with an improved outcome. Inhaled nitric oxide and surfactant therapy have been shown to improve oxygenation, but positive survival benefits are not observed.[9] Surfactant therapy can be lifesaving in infants with respiratory distress syndrome, and modification of surfactant composition and administration technique trials are ongoing.[10,11] Cytokine blocking agents have not been effective despite initial early promise. Intravenous β_2-agonists have been shown to effectively lower lung water in the β-Agonist Lung Injury Trial (BALTI),[12] and both positive fluid balance and high tidal volumes have been associated with a worse outcome.[13] A major breakthrough in the treatment of patients with ARDS is the use of lower tidal volumes in mechanical ventilation, which have been associated with less ventilator-induced lung injury and improved patient outcomes.[14] Most guidelines include limiting fluid balance to prevent overhydration, limiting ventilator-induced lung injury by limiting tidal volumes, using appropriate positive end-expiratory pressure (PEEP), and preventing other complications of critical illness.[15,16]

Treatment with activated protein C, which has been effective in sepsis, is being evaluated for ARDS in a phase II clinical trial. The Prospective, Randomized Phase II Clinical Trial of Activated Protein C (Xigris) Versus Placebo for the Treatment of Acute Lung Injury is sponsored by the National Heart, Lung, and Blood Institute with an expected completion date of 2008. A variety of other trials evaluating other pharmacologic and ventilatory maneuvers including surfactant, inhaled nitric oxide, and granulocyte-macrophage colony-stimulating factor are recruiting patients, and further information can be found at www.clinicaltrials.gov.

Resolution of ARDS occurs in an orderly fashion, similar to repair in any other tissue. First, excessive fluid and proteins (soluble and insoluble) are removed from the airways and alveoli. Next the type II alveolar epithelial cells must repopulate the epithelial lining, and the abnormal interstitium must restore its normal matrix. Finally, the damaged endothelium must be repaired to restore blood flow, and unnecessary or residual cellular components must be removed.[4,17]

If recovery is incomplete, persistent deficiencies in lung function may remain. Most recovery occurs over the first 3 months following extubation, with some additional recovery over the first year.[18] Quality of life of survivors is typically good, although depending on the concurrent critical illness or injury, there may be persistent abnormalities.[18] Some long-term human survivors of critical illness develop psychologic sequelae and may require ongoing therapy to regain their predisease state.

24.4 CANINE PERSPECTIVE

ALI and ARDS are recognized with far less frequency in critically ill dogs than in people, although several case reports suggest a similar association with critical illnesses.[19-22] Parent and colleagues were the first to comprehensively describe the clinical characteristics and course of 19 dogs identified with ARDS on necropsy in 1996.[23,24] Risk factors identified for dogs included pneumonia, sepsis, and shock. Several other case reports have highlighted the histopathologic appearance of ARDS in dogs with a variety of critical illnesses.[19-22] Campbell and King described 10 dogs receiving mechanical ventilatory support for pulmonary contusions; many (if not all) of the dogs surviving the initial 24 hours likely had ARDS.[25] Other reviews on ventilatory management have also described dogs ventilated for respiratory failure that likely met the criteria for ARDS, albeit this was not definitively stated, as an underlying cause.[26,27] Finally, in 2005 Walker and colleagues described the recovery from ALI in a dog with anaphylaxis associated with multiple bee stings.[28]

Most veterinary critical care specialists appear to agree that ARDS exists as a clinical entity in dogs. However, because of the lack of a consensus statement in dogs and difficulty at times in excluding other causes of respiratory distress, the actual incidence remains unclear. In some instances, such as with severe pulmonary contusion, it may be easier to apply the diagnosis ARDS to the patient still in respiratory distress 72 hours after onset, and in others, such as with aspiration pneumonia, it may be difficult to ascertain if ALI has developed or if recurrent aspiration has occurred. Proposed criteria for defining canine ALI and ARDS are listed in Box 24-1.

Recommendations for the treatment of potential ALI-ARDS in dogs focuses on eliminating other causes that may be more treatable. Thoracic radiographs should be evaluated for diffuse bilateral infiltrates. A sample for arterial
blood gas analysis should be evaluated for hypoxemia and for calculation of the alveolar-arterial gradient. If the 103
animal is extremely stressed or experiencing marked respiratory distress, sampling for an arterial blood gas should 104
be postponed so as not to risk causing further compromise or even cardiopulmonary arrest. Similarly, in a dog that is experiencing severe respiratory distress, supplemental oxygen delivery should not be interrupted to make interpretation of blood gases more straightforward.

24.4.1

Box 24-1 Proposed Criteria for Identification of ALI and ARDS in Dogs

- Preexisting severe acute critical illness or injury (pulmonary or extrapulmonary)
- Increased respiratory rate and effort
- Bilateral pulmonary infiltrates on thoracic radiographs
- Significant hypoxemia defined as PaO_2/FiO_2 of 200 to 300 (ALI)*
- PaO_2/FiO_2 of less than 200 (ARDS)*
- No evidence of left atrial hypertension as assessed via either echocardiography or pulmonary artery catheterization

ALI, Acute lung injury; *ARDS,* acute respiratory distress syndrome.

* In some small or uncooperative patients it may be difficult to obtain an arterial blood gas sample. Although pulse oximetry is not a replacement for arterial blood gas analysis, marked desaturation (e.g., <90%) should be considered indicative of severe hypoxemia and appropriate measures taken.

Volume overload and congestive heart failure should be excluded by echocardiogram. Bacterial pneumonia should be treated aggressively with antibiotics effective against hospital-acquired organisms. Pulmonary thromboembolism should be considered, and patients of concern should be evaluated via echocardiogram, computed tomography, D-dimers, or other means. If pulmonary thromboembolism is suspected, anticoagulant therapy should be initiated if clinically advisable. Positive-pressure ventilation with PEEP is the mainstay of support for the dog with ALI or ARDS. Suggested strategies for ventilatory management of animals with ARDS are largely derived from human data; these have not been evaluated comprehensively in clinical veterinary patients.[29] Sometimes less severely affected dogs may be treated with cage rest and supplemental oxygen.

Recovery from lung injury occurs over weeks; thus severe decreases in pulmonary compliance (or increases in inspiratory pressures) should be considered ominous in dogs being supported with mechanical ventilation. No specific therapy for ALI-ARDS is available, and care is largely supportive. Limiting ventilator-induced lung injury is an essential aspect of mechanical ventilation, but optimal tidal volumes for dogs with ARDS have not been established. Because of the substantial difference in thoracic cavity dimensions (e.g., Pug versus an Irish Setter), it may be that ultimately breed- or body type-specific recommendations will be developed. For the time being, lung-protective ventilation strategies in which tidal volume is minimized in conjunction with moderate to high PEEP levels are recommended for ALI-ARDS patients (see Chapters 213 and 214, Basic Mechanical Ventilation and Advanced Mechanical Ventilation, respectively). Given the significant financial and emotional commitment required to support a critically ill dog undergoing mechanical ventilation, realistic and frequent patient evaluations are recommended.

As we expand our understanding of the pathophysiology and our experience with ARDS-ALI in dogs increases, future therapies and management strategies may be developed and tested to reduce morbidity and improve survival. An important first step involves increasing awareness and recognition of this disease entity in dogs. Efforts to better define this syndrome in dogs are warranted to allow comparison of any forthcoming case series and clinical trials.

24.5 FELINE PERSPECTIVE

There is even less known about ALI-ARDS in cats than in dogs. A single abstract describes 65 cats with ALI-ARDS identified by histopathology at postmortem examination.[30] This report suggests that the disease process in cats is analogous to that in dogs and humans. In the absence of evidence to the contrary, diagnostic and therapeutic treatment of feline patients is considered similar to that of the canine patient. Hopefully there will be further reports and investigations in the near future to improve our understanding of ALI-ARDS in cats.

24.6 SUGGESTED FURTHER READING*

DG Ashbaugh, DB Bigelow, TL Petty, BE Levine: Acute respiratory distress in adults. *Lancet*. **2**, 1967, 319, *The seminal description of ARDS in adult human patients that led to establishment of this disease entity as a major cause of death in critically ill patients.*

ER Mueller: Suggested strategies for ventilatory management of veterinary patients with acute respiratory distress syndrome. *J Vet Emerg Crit Care*. **11**, 2001, 191, *A review of ventilation strategies used in people and extrapolations for use in veterinary patients.*

C Parent, LG King, TJ Van Winkle, et al.: Respiratory function and treatment in dogs with acute respiratory distress syndrome: 19 cases (1985-1993). *J Am Vet Med Assoc*. **208**, 1996, 1428, *The first comprehensive review of treatment strategies in dogs with ARDS.*

C Parent, LG King, LM Walker, et al.: Clinical and clinicopathologic findings in dogs with acute respiratory distress syndrome: 19 cases (1985-1993). *J Am Vet Med Assoc*. **208**, 1996, 1419, *The first comprehensive review of dogs with ARDS.*

AB Weinacker, LT Vaszar: Acute respiratory distress syndrome: physiology and new management strategies. *Annu Rev Med*. **52**, 2001, 221, *An excellent review of the pathophysiology and treatment strategies for ARDS.*

* See the CD-ROM for a complete list of references

25 Chapter 25 Pulmonary Contusions and Hemorrhage

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25.1 KEY POINTS

- Pulmonary contusions occur commonly in patients following blunt chest trauma. The contusions consist of interstitial and alveolar hemorrhage, accompanied by parenchymal destruction that starts immediately following the impact but can worsen for 24 to 48 hours after injury.
- The lesions typically resolve within 3 to 10 days, unless complications such as pneumonia or acute respiratory distress syndrome ensue.
- Clinical signs may be acute and severe or may develop progressively over several hours following trauma.
- The diagnosis of pulmonary contusions is based on a history of trauma and the presence of respiratory signs, ranging from tachypnea to respiratory distress, in conjunction with compatible blood gas abnormalities and characteristic changes on thoracic radiographs.
- Treatment of patients with pulmonary contusions is supportive and consists of oxygen therapy, judicious fluid administration, and analgesia for concurrent thoracic wall injuries. Ventilatory support may be necessary in severe cases.
- Less common causes of pulmonary hemorrhage include coagulopathies, thromboembolic disease, infectious disease (viral, bacterial, and parasitic), exercise-induced hemorrhage, and neoplasia.
- Treatment of atraumatic pulmonary hemorrhage is directed toward the underlying disease in addition to supporting respiratory and ventilatory function.

25.2 INTRODUCTION

Pulmonary contusions consist of pulmonary interstitial and alveolar hemorrhage and edema associated with blunt chest trauma, usually after a compression-decompression injury of the thoracic cage. Such injury is most commonly associated with motor vehicle trauma[1] and high-rise falls[2] in cats in urban areas. Other causes include animal interactions (e.g., horse kicks), human abuse, and shock waves from explosions.

Thoracic trauma has been reported in 34%,[3] 38.9%,[4] and 57%[5] of dogs and 17% of cats[4] that sustained limb fractures in road traffic accidents. Pulmonary contusions were the most prevalent lesion in roughly 50% of animals with thoracic injuries, although patients may display few clinical signs associated with the contusions. They may occur as an isolated abnormality or in combination with other thoracic injuries including pneumothorax, pleural effusion, rib fractures, diaphragmatic rupture, cardiac arrhythmias, and pericardial effusion.[4,6] Pulmonary contusions may be the most significant abnormality present; in one study, only 32% of dogs had concurrent fractures or luxations.[7] It is worth noting that in another study 79% of the dogs with abnormal thoracic radiographic findings or low arterial partial pressure of oxygen (PaO_2) had no physical findings that were suggestive of thoracic injury on initial examination.[5]

The clinical manifestations of pulmonary contusions, as in any thoracic trauma, can be acute and lead to immediate, severe respiratory distress, or may develop progressively over several hours after the injury. Radiographic changes may also be delayed. Because aggressive fluid therapy and general anesthesia have the potential to worsen contusions, the emergency clinician must not discount the possibility of their presence when evaluating more dramatic injuries, even if clinical signs of thoracic injury or respiratory distress are not apparent initially.

25.3 PATHOPHYSIOLOGY AND PATHOLOGY

Pulmonary contusions result from the release of direct or indirect energy within the lung. High-velocity missiles and blasts also lead to pulmonary contusions as shock waves pass through the parenchymal tissue and lead to bleeding into the alveolar spaces and disruption of normal lung structure and function. Several mechanisms have been postulated as important in the etiology of pulmonary contusion.[8]

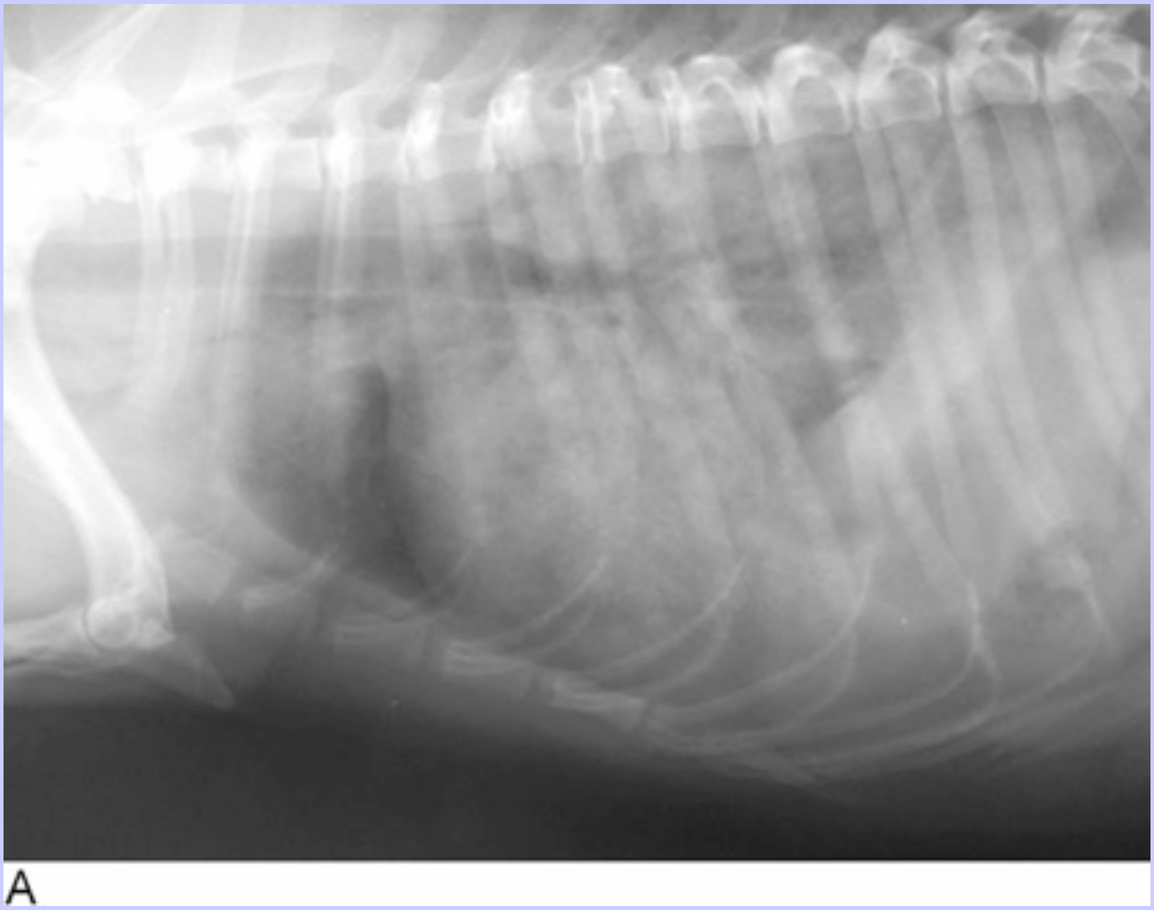
Due to the compressible nature of the thoracic cage, acute compression and subsequent expansion lead to transmission of mechanical forces and energy to the pulmonary parenchyma. As a result, the lung is injured directly by the increased pressure in the so-called spalling effect, a shearing or bursting phenomenon that occurs at gas-liquid interfaces and that may disrupt the alveolus at the point of initial contact with shock waves. The “inertial effect” that occurs when low-density alveolar tissue is stripped from heavier hilar structures as they accelerate at different rates results in both mechanical tearing and laceration of the lungs. Finally, an “implosion effect,” resulting from rebound or overexpansion of gas bubbles after a pressure wave passes, can lead to tearing of the pulmonary parenchyma from excess distention.[9,10] The parenchyma may also be injured by the displacement of fractured ribs. Subsequent hemorrhage results in bronchospasm, increased mucus production, and alveolar collapse due to decreased production of surfactant.[11]

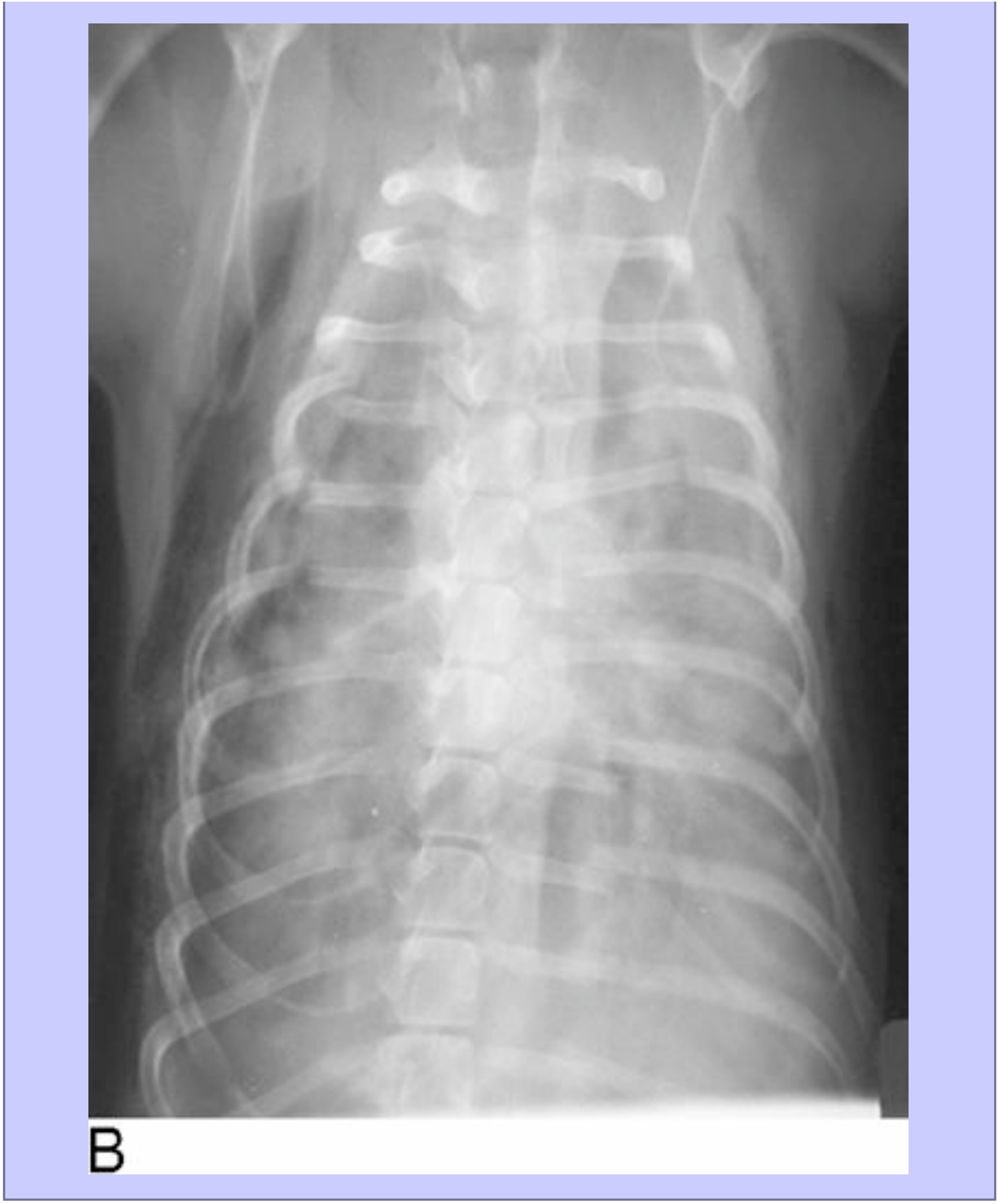
Damage to the lung leads to complex changes in respiratory function. The parenchymal damage causes ventilation-perfusion mismatch as the alveoli are flooded with blood and underventilated. There is also an increase in lung water due to the accumulation of protein-rich edema, subsequently decreasing lung compliance.[12] However, the initial vasoconstriction in response to local hypoxia (hypoxic pulmonary vasoconstriction) may be followed by a further decrease in local perfusion secondary to vascular congestion and thrombosis. This results in reduced perfusion to the unventilated lung, thus reducing the shunt fraction. The patient subsequently displays dyspnea from hypoxemia. Either hypocarbia or hypercarbia may be present depending on the severity of the contusions and the effects of concurrent injuries on ventilation.

In animals that survive the initial hours, the respiratory derangements associated with pulmonary contusions usually resolve in 3 to 7 days, but delayed deterioration may occur. Delayed clinical signs of pulmonary dysfunction may occur from complications such as bacterial pneumonia or acute respiratory distress syndrome (ARDS) secondary to the local or systemic inflammatory response.[11] The frequency of these complications has not been well described in dogs and cats. In humans, pulmonary contusions cause severe immunodysfunction both locally and systemically, and this immunosuppression is associated with a decreased survival rate if a septic insult occurs.[13]

Histologic progression of pulmonary contusions has been demonstrated in a canine experimental model.[14] Immediate interstitial hemorrhage is followed by interstitial edema and infiltration of monocytes and neutrophils during the first few hours. Twenty-four hours after injury, the alveoli and smaller airways have been filled with protein, red blood cells, and inflammatory cells. At this stage, the normal architecture has been lost and edema is severe. Alveoli adjacent to the affected region remain normally perfused, but they are less compliant due to the edema and disruption of the surfactant layer. Thus, they are poorly ventilated, which leads to an increase in ventilation-perfusion mismatch.[12,15-17] Furthermore, experimental studies in pigs have demonstrated that local pulmonary contusions may lead to generalized pulmonary dysfunction secondary to impaired surfactant activity and a subsequent decrease in alveolar diameter.[18] Forty-eight hours after injury, healing has started and the lymphatic vessels are dilated and filled with protein. The parenchyma and affected airways contain fibrin, cellular debris, granules from type II alveolar cells, neutrophils, and macrophages.[12] Another study found that within 7 to 10 days post trauma, canine lungs were almost completely healed with little scarring.[16]

Figure 25-1 Lateral **(A)** and dorsoventral **(B)** radiographs showing the characteristic appearance of pulmonary contusions. Note the diffuse alveolar pattern. It is common to see additional radiographic abnormalities, such as multiple rib fractures, subcutaneous emphysema, pneumomediastinum, and pneumothorax, as seen in this case.




B

25.4 DIAGNOSIS

25.4.1 Physical Findings

Clinically, patients have tachypnea or dyspnea dependent on the severity of the contusions and the time between injury and arrival at the veterinary clinic. Auscultation findings may be normal, or increased breath sounds and crackles can be present and may worsen over the initial 24-hour period. These abnormalities are often asymmetric or truly unilateral. Lung auscultation findings can be more difficult to interpret when concurrent conditions, such as pneumothorax, are present. Therefore frequent monitoring of respiratory rate, effort, and pulmonary auscultation is warranted. Hemoptysis (the expectoration of blood from distal to the larynx) is present in a high proportion of human patients. It appears to be an uncommon finding in small animals but is usually associated with severe lesions.

Because there is a high incidence of thoracic trauma associated with skeletal injuries and respiratory symptoms may be absent or masked initially, the clinician should maintain a high index of suspicion for contusions in any traumatized patient.

25.4.2 Imaging: Radiology and Computed Tomography

Dyspneic patients should undergo stabilization before imaging is attempted. Animals that sustain thoracic trauma may have multiple thoracic injuries, making a precise diagnosis based on the physical examination alone challenging. Imaging studies may be helpful in identifying the injuries. However, as with all dyspneic patients, the risk-to-benefit ratio of the imaging procedure should be considered carefully.

Radiographic changes in patients with pulmonary contusions consist of areas of patchy or diffuse interstitial or alveolar lung infiltrates that can be either localized or generalized (Figure 25-1). Radiographic changes may lag 106
behind clinical signs by 12 to 24 hours and therefore "normal" radiographic findings may be seen in animals 107
with pulmonary contusions. Patients with more severe radiographic changes initially may require a longer duration of oxygen supplementation and longer hospitalization times. However, the relationship between severity of the contusion based on radiographic changes and survival has not been established.[7]

Although computerized tomography (CT) has been shown experimentally to be more sensitive for detecting initial lesions and accurately reflecting the extent of the lesion than standard radiographic techniques, lack of availability and the need for sedation or anesthesia in a traumatized patient have limited its use. An experimental canine model of pulmonary contusions found that a CT scan enabled detection of 100% of the pulmonary lesions, but initial thoracic radiographs failed to visualize them. In addition, 21% were still not visible radiographically after 6 hours. Also, CT imaging underestimated the extent of the lesions in only 8% of the animals, whereas thoracic radiography underestimated the extent in 58% of the animals.[19]

25.4.3 Blood Gas Analysis and Pulse Oximetry

Arterial blood gas analysis is the most objective method for assessing and monitoring the physiologic effects of thoracic trauma (see Chapter 208, Blood Gas and Oximetry Monitoring). Clinical data in dogs reveal a high incidence of hypoxemia, however it is usually mild to moderate.[5,7] This may be because many of the most severe cases will die before arriving at the veterinary clinic. Either hypocarbia or hypercarbia may be seen, depending on the severity of the parenchymal injury, the nature of concurrent thoracic injuries, and other factors such as pain, distress, and the effect of concurrent metabolic acid-base derangements.

In humans, the arterial oxygen tension-to-fractional concentration of inspired oxygen ratio (PaO_2/FiO_2) is directly correlated with the volume of contused lung for the first 24 hours after injury, although this correlation is not consistent beyond 1 week.[20] Whether this association exists in small animal patients is unknown.

Although pulse oximetry has some limitations, it may be a useful quantitative assessment of oxygenation in cases in which an arterial blood gas analysis is not possible (i.e., cats). It is a less accurate indicator of impaired oxygenation, does not provide a measure of ventilation, and reliable measurements can be difficult to obtain in patients that are in shock. It is important to ensure that the pulse oximeter is reading an accurate pulse rate in order to acquire an accurate reading. A reading of less than 95% indicates hypoxemia and values less than 90% are consistent with severe hypoxemia.

25.5 MANAGEMENT

25.5.1 Initial Approach

Management of pulmonary contusions is supportive. Initial triage and major body system assessment should be done in any traumatized patient, and injuries should be ranked and managed based on their threat to patient life (see Chapter 2, Patient Triage). Prehospital management rarely occurs. However, the animal should be transported to the clinic lying in its preferred posture or kept in sternal recumbency if possible.

Oxygen therapy, judicious fluid therapy, and adequate analgesia are essential components of patient management.

25.5.2 Oxygen Therapy and Ventilation

Oxygen should be administered to all dyspneic patients (see Chapter 19, Oxygen Therapy). Noninvasive methods such as flow-by, nasal oxygen delivery, or oxygen cages and hoods are commonly used. In severely affected cases, intubation and ventilation may be necessary (see Chapters 213 and 214, Basic Mechanical Ventilation and Advanced Mechanical Ventilation, respectively). This decision should be made based on the severity of the dyspnea and an assessment of arterial blood gas values, if possible.

In people, pressure-controlled ventilation with positive end-expiratory pressure is the preferred method of mechanical ventilation.[21] One canine study examined 10 dogs with pulmonary contusions that required positive-pressure ventilation and found that 50% of the dogs benefited from this therapy, and animals that weighed more than 25 kg were more likely to survive.[22] Alveolar recruitment strategies and the use of low tidal volumes have been shown to increase both oxygenation and lung aeration in humans with severe chest trauma,[23] although similar studies in dogs and cats are lacking.

Other advanced ventilatory techniques such as jet ventilation, selective bronchial intubation, dual-lung ventilation, and extracorporeal membrane oxygenation may prove useful, but are not used routinely in the veterinary field.

25.5.3 Fluid Therapy

Many patients with thoracic trauma will have some degree of concurrent hypovolemic shock. The debate on optimal fluid therapy in trauma and shock has yet to be resolved, however it seems that optimizing fluid therapy to maintain adequate perfusion while avoiding overzealous administration is likely to give the best results. In any patient with multiple trauma, the clinician must prioritize treatment decisions based on which major body system is most severely affected.

As with any patient in noncardiogenic shock, several fluid options are available, and the fluid type and administration strategy chosen must take into account both the cardiovascular and pulmonary changes present (see Chapter 65, Shock Fluids and Fluid Challenge). Regardless of the type of fluid chosen, increases in pulmonary capillary hydrostatic pressure may lead to increased fluid extravasation into the alveoli and worsening of pulmonary function. The clinician should aim to optimize tissue perfusion while avoiding excessive fluid administration that could worsen the pulmonary edema and hemorrhage. Careful monitoring and tailoring of the fluid protocol to the patient are preferable to administering preset volumes and rates. Replacement crystalloids are the most economical fluids and are at least as effective as colloids for resuscitation of the patient in shock.[24,25] Despite the smaller volumes administered, hypertonic saline showed no benefit over isotonic solutions in the management of pulmonary contusions in experimental pigs.[26] Blood products and synthetic colloids may contribute to worsening pulmonary edema if they leak into the airways or interstitium. Hemoglobin-based oxygen carriers, when compared with 0.9% saline, led to poorer oxygenation and more extensive pulmonary lesions in a porcine model of pulmonary contusion and hemorrhage.[27]

In conclusion, although fluid restriction is not indicated, caution should be exercised in administering intravenous fluids to shock patients with suspected pulmonary contusions. Patients should be monitored carefully to detect any worsening of pulmonary function during fluid administration and fluid rates adjusted accordingly.

25.5.4 Analgesia

Hypoventilation due to pain secondary to concurrent injuries can be severe and should be managed proactively with analgesics (see Chapters 161 and 164, Pain and Sedation Assessment and Analgesia and Constant Rate Infusions, respectively). Ideally, drugs that cause minimal impairment of cardiac and respiratory functions should be used. Intercostal, intrapleural, and epidural analgesic administration can be used in conjunction with, or as an alternative to, systemic opioid administration.

25.5.5 Antibiotics

Based on the reported low incidence of pneumonia after pulmonary contusions (1%),[7] indiscriminate use of antimicrobial agents should be avoided to limit bacterial resistance. In the small number of patients that do develop bacterial pneumonia, antibiotic therapy should be based on culture and sensitivity results of airway cytology (see Chapter 22, Pneumonia).

25.5.6 Glucocorticoids

There are few supportive data for glucocorticoid use. Although some animal studies have shown a reduction in hypoxemia and lesion size with their use,[28] others have shown no benefit.[29] Due to their potential deleterious effects, including increased susceptibility to infection and gastrointestinal ulceration, and the lack of positive effects on outcome, these agents are not recommended in the routine management of pulmonary contusions.

25.6 PROGNOSIS AND OUTCOME

Outcome is related to the severity of pulmonary contusions as well as any coexisting thoracic and extrathoracic lesions. Survival rates of 82% have been described,[7] although the real survival rate may be lower because some of the most severely affected animals die before reaching a veterinary facility or before a diagnosis is made. Patients may require hospitalization for periods ranging from a few hours to several days, and oxygen supplementation can be required for several days to weeks.

In more severely affected patients, two retrospective studies have shown that approximately 30% of dogs requiring mechanical ventilation for contusions survived to discharge.[7,22] It is possible that newer lung-protective ventilatory strategies could improve outcomes (see Chapter 26, Ventilator - Associated Lung Injury).

Although the long-term prognosis for animals with pulmonary contusions has not been investigated, most animals that survive to discharge do not appear to have residual long-term sequelae.

25.7 ATRAUMATIC PULMONARY HEMORRHAGE

Atraumatic pulmonary hemorrhage may occur secondary to a diverse range of disease conditions (Table 25-1).

Although hemoptysis may occur in animals with pulmonary hemorrhage, it is an uncommon initial finding in small animals,[30] and pulmonary hemorrhage cannot be ruled out based on the absence of this symptom. In a population of cats undergoing airway cytologic analysis for a variety of disease conditions, pulmonary hemorrhage was identified in 63% of cases. It was not reported how many of them had hemoptysis.[31]

Table 25-1 Etiology of Atraumatic Pulmonary Hemorrhage

Infectious	Bacterial	Leptospirosis
	Fungal	—
	Mycoplasmal	—
	Parasitic	Heartworm (*Dirofilaria* spp) Lungworm *(Angiostrongylus vasorum)*
	Viral	—
Coagulation abnormalities	Defects of primary hemostasis	Thrombocytopathia Severe thrombocytopeniaUremia
	Defects of secondary hemostasis	Anticoagulant rodenticides von Willebrand diseaseHemophilia
	Thromboembolism	Cushing's disease Diabetes mellitusNephrotic syndromeGlucocorticoid therapy
Cardiac	Heart failure Pulmonary hypertension	—
Neoplasia	PrimaryMetastatic	—
Anatomic	Lung lobe torsion	—
Environmental	Aspiration pneumoniaForeign bodies	—
Miscellaneous	Exercise-induced pulmonary hemorrhage in racing greyhounds	—
Iatrogenic	Fine-needle aspirationPercutaneous biopsy	—

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25.8 DIAGNOSTIC EVALUATION

Pulmonary hemorrhage is identified by hemoptysis or hemorrhage on cytologic samples from tracheal, bronchial, or bronchoalveolar washes. The emergency clinician must be careful to distinguish true hemoptysis from hematemesis or bleeding from a source cranial to the larynx (nasal cavity, oropharynx). When using cytology specimens, acute hemorrhage is defined by presence of red blood cells and white blood cells in proportions similar to those in peripheral blood. Platelets may be present but tend to disappear within minutes after the hemorrhagic event. Within minutes to hours, erythrophagocytosis is present within the macrophages. Considering the diverse range of differential diagnoses, a thorough and careful diagnostic evaluation including full history, diligent physical examination, as well as clinicopathologic testing and imaging may be required to reach the correct diagnosis.

Historical information that suggests certain diagnoses may include exposure to toxins such as rodenticides or animals living in or having traveled to areas with a high incidence of certain infectious diseases (e.g., heartworm or lungworm). The influence of any concurrent drug therapy should be considered, such as high doses of glucocorticoids, especially in patients that are at risk for pulmonary thromboembolism. Historical information may also be suggestive of chronic medical conditions and may guide and inform further testing. The patient's signalment may suggest an increased possibility of certain coagulopathies, such as von Willebrand disease in Doberman Pinschers.

The physical examination of animals with pulmonary hemorrhage may reveal clinical signs limited to the respiratory system including hemoptysis, dyspnea, tachypnea, cough, and abnormal auscultation findings. Auscultation findings are variable but may include focal or generalized harsh lung sounds progressing to crackles, focal muffled lung sounds corresponding to areas with consolidation or complete filling of the small airways, or wheezes. Heart murmurs or cardiac arrhythmias may also be noted and may suggest a cardiogenic cause for the pulmonary hemorrhage. However, because pulmonary hemorrhage may occur secondary to systemic disease, a full physical examination is mandatory. The presence of petechiae or ecchymoses should prompt the investigation of a bleeding disorder, whereas an elevated body temperature may suggest infectious or neoplastic disease.

Further diagnostic tests will be suggested by the patient's history and physical examination but may include a CBC, biochemical profile, coagulogram, urinalysis, and imaging techniques. An arterial blood gas analysis will provide the best evaluation of the functional impairment of the respiratory system and may reveal hypoxemia, hypocarbia (or hypercarbia in severe cases), and an increased alveolar–arterial gradient. However, in animals with suspected or confirmed pulmonary hemorrhage, arterial sampling should be avoided until clotting times and platelet numbers and function have been assessed. Animals with chronic diseases such as pulmonary neoplasia, chronic bronchitis, or pneumonia may have metabolic compensation for changes in arterial carbon dioxide tensions, whereas acutely affected animals often have uncompensated changes in acid-base status.

Thoracic radiographs may reveal an interstitial, alveolar, or mixed pattern, with a focal, patchy, or diffuse distribution. A peripheral interstitial and alveolar pattern in a young to middle-aged dog is a characteristic finding in *Angiostrongylus vasorum* infestation.[32] The cardiac silhouette may be enlarged and there might be signs of pulmonary congestion in cases of congestive heart failure or *Dirofilaria* spp infestation. If cardiac disease is suspected, echocardiography is the test of choice for characterization of the disease.

Hematology findings may be unremarkable or may show changes suggestive of the underlying diagnosis, including normocytic normochromic anemia in case of chronic disease, eosinophilia with parasitic disease, and neutrophilia with or without a left shift in cases of inflammatory disease. Platelet numbers may be normal, mildly to moderately reduced (e.g., in disseminated intravascular coagulation, angiostrongylosis, and some cases of thromboembolism), or severely reduced (e.g., in immune-mediated thrombocytopenia). If platelet numbers are adequate but petechiae are present, thrombocytopathia may be present and a buccal mucosal bleeding time should be performed (see Chapter 118, Bleeding Disorders).

Clotting times (prothrombin time and activated partial thromboplastin time) are prolonged in animals with coagulopathy. The prothrombin time is markedly prolonged in animals with anticoagulant rodenticide poisoning. Increases in fibrinogen degradation products or d-dimers may suggest pulmonary thromboembolism, although a CT scan with angiography is more definitive.[33]

A fecal Baermann analysis should be performed if *A. vasorum* or other lungworm infections are suspected. Antigen or antibody detection tests for heartworm are indicated in dogs or cats living in, or traveling to, endemic areas.

25.9 TREATMENT

Treatment will ultimately need to be directed toward the underlying disease process. If the degree of respiratory compromise is marked, it may be necessary to use supportive or empiric therapy while the diagnosis is pursued. Oxygen should be administered to any dyspneic patient, and in particular to those animals showing hypoxemia on arterial blood gas analysis or low pulse oximetry readings. If noninvasive oxygen supplementation does not restore adequate oxygen levels, severe hypercarbia is present, or if the patient displays significant dyspnea with impending fatigue, positive-pressure ventilation may be required (see Chapter 213, Basic Mechanical Ventilation). Fluid therapy should be tailored to each animal's needs based on the cardiovascular and respiratory status, as with pulmonary contusions. Analgesia and sedation should also be used when indicated by an animal's clinical status. It is often necessary to institute empiric antimicrobial therapy on the basis of a strong clinical suspicion while diagnostic test results are pending.

25.10 PROGNOSIS AND OUTCOME

Prognosis and long-term outcome will depend largely on the extent and severity of the process on admission, and on the exact nature of the cause. However, a mortality rate of up to 25%[30] has been reported in the short term, with more cases dying or being euthanized as a result of the disease in less than 6 months. It is difficult to predict whether there will be any long-term impairment of function, but this will likely depend on the underlying disease and its severity. Hence, owners should be given a grave to guarded prognosis until a definitive diagnosis is reached. 109

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25.11 SUGGESTED FURTHER READING[*]

N Bailiff, C Norris: Clinical signs, clinicopathological findings, etiology, and outcome associated with hemoptysis in dogs: 36 cases (1990–1999). *J Am Anim Hosp Assoc*. **38**, 2002, 125–133, *Retrospective study on hemoptysis that offers a very good overview. However, the reader should be aware of the likely etiologic bias due to the caseload in a university hospital in which all animals were from the same geographic region.*

S Cohn: Pulmonary contusions: review of the clinical entity. *J Trauma*. **45**, 1997, 973–979, *One of the most thorough reviews on pulmonary contusions in people. Most information is still useful, although areas such as fluid therapy and ventilation strategies have changed since the publication time.*

R Moseley, J Vernick, D Doty: Response to blunt chest injury: a new experimental model. *J Trauma*. **101**, 1970, 673–683, *Very interesting experimental study in a canine model that describes the progressive radiographic and pathologic changes, in addition to alterations in blood gases, respiratory mechanics, and hemodynamics over time.*

L Powell, E Rozanski, A Tidwell, et al.: A retrospective analysis of pulmonary contusion secondary to motor vehicular accidents in 143 dogs: 1994–1997. *J Vet Emerg Crit Care*. **9**, 1999, 127–136, *Large retrospective on pulmonary contusions in dogs that provides very useful information but lacks detail in some areas (probably due to its retrospective nature).*

N Sigrist, M Doherr, D Spreng: Clinical findings and diagnostic value of post-traumatic thoracic radiographs in dogs and cats with blunt trauma. *J Vet Emerg Crit Care*. **14**, 2004, 259–268, *The most recent and extensive retrospective on thoracic imaging for dogs and cats that sustain trauma.*

[*] See the CD-ROM for a complete list of references

26 Chapter 26 Ventilator-Associated Lung Injury

Rebecca S. Syring, DVM, DACVECC

26.1 KEY POINTS

- Mechanical ventilation is often needed for support of critically ill patients with pulmonary dysfunction. However, mechanical ventilation can perpetuate or induce a form of lung injury, referred to as *ventilator-associated lung injury (VALI)*.
- VALI can occur in both healthy lungs and diseased lungs with prolonged mechanical ventilation.
- Overdistention of alveoli, often referred to as *volutrauma,* mechanical disruption of pulmonary tissues as a result of pressure, often referred to as *barotrauma,* and repetitive alveolar opening and collapse of alveoli, often referred to as *atelectrauma,* are the chief components of VALI.
- Therapeutic goals that may reduce the incidence of VALI include limited plateau pressures (<30 to 35 cm H_2O) to reduce the risk for barotrauma, limited tidal volume (≈6 ml/kg) to reduce alveolar overdistention, and positive end-expiratory pressure (PEEP) above the critical closing pressure to prevent cyclic recruitment of alveoli.

26.2 INTRODUCTION

Mechanical ventilation is being used with increasing frequency to support veterinary patients with respiratory failure secondary to impaired oxygenation or ventilation (see Chapter 213, Basic Mechanical Ventilation).[1-5] Common reasons for impaired oxygenation requiring mechanical ventilation include pneumonia, cardiogenic pulmonary edema, and acute respiratory distress syndrome (ARDS). Impaired ventilation, or the inability to eliminate carbon dioxide through the lungs, can be seen as a result of an impaired ventilatory drive secondary to intracranial disease, neuromuscular disease, or as a sequela to respiratory fatigue from increased work of breathing or severe pulmonary disease.

Two of the most common causes of respiratory failure requiring mechanical ventilation in human medicine are ARDS and acute lung injury (ALI). ARDS represents a diffuse, inflammatory pulmonary disorder resulting from a wide variety of clinical conditions, both intrapulmonary and systemic, and is clinically characterized by a sudden onset, bilateral alveolar infiltrates, an arterial-to-inspired oxygen tension ratio (PaO_2-to-FiO_2) under 200 mm Hg, and the absence of left-sided heart failure. ALI describes a similar clinical scenario, however pulmonary dysfunction is marginally better, with PaO_2-to-FiO_2 ratios of 200 to 300 mm Hg. These syndromes have been recognized in both dogs and cats with naturally occurring disease (see Chapter 24, Acute Lung Injury and Acute Respiratory Distress Syndrome).[6-8] Although mechanical ventilation is vital for the support of respiratory function in patients with ARDS and other causes of respiratory failure, mechanical ventilation itself can potentiate or even induce lung injury.

26.3 VENTILATOR-INDUCED LUNG INJURY AND VENTILATOR-ASSOCIATED LUNG INJURY

Ventilator-induced lung injury (VILI) is characterized by increased capillary permeability, pulmonary edema, cellular injury, and diffuse structural damage to alveoli that is clinically indistinguishable from the damage that occurs in ARDS. For this reason, the term *VILI* is often restricted to describe pulmonary changes as a result of mechanical ventilation in experimental animal models. Ventilator-associated lung injury (VALI) describes a lung injury resembling ARDS that develops or worsens during the course of mechanical ventilation in clinical patients—this injury can only be associated with ventilation, rather than saying that it is definitively caused by ventilation, because the underlying disease process may be responsible for progression of lung injury.[9] During the past decade, positive-pressure ventilation strategies have evolved based on experimental evidence of VILI and clinical trials studying the effects of ventilator management on VALI.

The role that positive-pressure ventilation plays in perpetuating lung injury is easiest to appreciate in studies of human patients who do not have ALI or ARDS at the onset of therapy. One study evaluated 332 human patients who did not fit the criteria for ALI prior to the onset of more than 48 hours of mechanical ventilation. In this study, 24% of these patients went on to develop ALI during the course of mechanical ventilation. Two of the risk factors identified for VALI in this study included larger day 1 tidal volumes (above 6 ml/kg) and a history of restrictive pulmonary disease which would result in reduced pulmonary compliance. Interestingly, larger tidal volumes were more likely to be used in presumed lower risk patients: those who were ventilated postoperatively, had lower predicted mortality rates, or had better gas exchange and pulmonary mechanics.[10] This emphasizes that ventilation, be it manual or mechanical, and the risk for VALI should never be taken lightly in any patient population.

26.4 PRIMARY CAUSES OF VALI

26.4.1 Barotrauma

The term *barotrauma* refers to the mechanical disruption of tissues as a result of pressure.[11] Pulmonary barotrauma occurs when excessive positive pressure accumulates within the proximal airways and ultimately alveoli, resulting in alveolar membrane rupture and accumulation of free air within the pleural space. During positive-pressure ventilation, pneumothoraces can progress rapidly, because the positive distending pressure promotes air leakage into the pleural space, and the air cannot escape when the thoracic cavity is closed. Left unmanaged, excessive intrapleural pressure develops and impairs not only pulmonary expansion and gas exchange, but also impedes venous return to the heart. Tension pneumothorax refers to a life-threatening condition in which respiratory and cardiac function are both significantly compromised as a result of elevated intrathoracic pressure from the accumulation of free air in the pleural space.

Prior to lung-protective ventilatory strategies, the incidence of barotrauma was as high as 40% to 60% in mechanically ventilated humans[12] and was reported in 50% of dogs with clinical symptoms of ARDS.[6] Since the advent of lung-protective ventilatory strategies in human patients with ARDS, barotrauma occurs much less frequently, ranging from 6% to 14%.[12] This lower incidence has been associated with the underlying disease process, with patients who have suffered multiple trauma and patients with reduced pulmonary compliance (<30 ml/cm H_2O) who are at greater risk for developing a pneumothorax after the onset of mechanical ventilation.[12] A study in cats requiring ventilatory support for a variety of reasons reported a 28% incidence of barotrauma, approximately half of which occurred despite peak inspiratory pressures below 25 cm H_2O.[1] A larger, more recent study in dogs and cats requiring mechanical ventilation for a variety of reasons reports the lowest incidence of barotrauma (6.6%).[1,4] This may represent adaptations of ventilatory strategies in veterinary medicine toward more lung-protective ventilation; however, because this study was not limited to patients with ARDS, it is difficult to compare it with previous studies.

26.4.2 Volutrauma

Volutrauma refers to lung injury occurring secondary to alveolar overdistention. Although volutrauma eventually can result in elevated airway pressures and air leak, lung injury can occur when barotrauma is absent. Instead, elevated transpulmonary pressure and alveolar overdistention can result in more subtle injuries to alveolar endothelial and epithelial cells. These changes include ultrastructural breaks in the cell membranes, intraalveolar hemorrhage, hyaline membrane formation, alveolar collapse, and proliferation of type II pneumocytes. Ultimately this results in increased permeability and high-protein pulmonary edema. In addition, capillary blood flow to the alveoli may be compromised secondary to excessive airway distention.

26.4.3 Atelectrauma

Atelectasis of dependent alveoli, which is relatively common in patients with ALI and ARDS, results in reduced functional residual capacity of the lungs. If collapsed alveoli are not recruited (opened up) during ventilation, when a set tidal volume is delivered it is distributed to a smaller portion of the lung, increasing the risk for volutrauma to open alveoli. Alternatively another component of VALI, referred to as *atelectrauma,* can occur if collapsed alveoli are recruited during inspiration but allowed to collapse during expiration (derecruitment). Atelectrauma has also been referred to as *cyclic recruitment, tidal recruitment,* and *repetitive alveolar collapse and expansion*.

The alveoli within and adjacent to atelectatic lung are subjected to excessive shearing forces in order to open these alveoli during ventilation.[13] These shearing forces and the cyclic recruitment and collapse of alveoli induce inflammatory mediator release within the lungs,[14] which can increase capillary leak and pulmonary edema, induce inflammatory cell influx, and upregulate the systemic inflammatory response.

26.5 VENTILATOR STRATEGIES TO AVOID VALI

The primary risk factor for barotrauma during mechanical ventilation is excessive proximal airway pressure. The incidence of barotrauma increases as higher plateau airway pressures are applied. Therefore efforts should be made to use the lowest plateau pressure that maintains oxygenation and ventilation within an acceptable range. When a cutoff of 35 cm H_2O was used as a plateau pressure, the risk for barotrauma was dramatically reduced in a review of data on ventilated humans.[12] With more severe pulmonary disease compliance often decreases, resulting in higher airway pressures for a given tidal volume. In order to avoid excessive airway pressures, alterations in other ventilator settings such as respiratory rate, PEEP, and inspiratory-to-expiratory ratio may be necessary to maintain oxygenation and ventilation at an acceptable plateau pressure (see Chapters 213 and 214, Basic Mechanical Ventilation and Advanced Mechanical Ventilation, respectively).

The risk for barotrauma also applies to manual ventilation during general anesthesia, a scenario in which detailed pulmonary function monitoring is uncommon. Care should be taken to avoid pressure accumulation in the anesthetic circuit either by keeping the pop-off valve open or by reducing oxygen flow rates (10 to 15 ml/kg/min) when the pop-off valve is partially or fully closed during low-flow anesthesia. In addition, during manual breaths one should pay attention to the maximum airway pressure generated in the anesthetic circuit. Airway pressures should not exceed 25 to 30 cm H_2O. If oxygenation cannot be maintained at or below this pressure, PEEP should be applied to recruit alveoli and minimize the need for higher airway pressures whenever possible.

Paying close attention to the absolute tidal volume delivered with volume-controlled ventilation or relative tidal volume with pressure-controlled ventilation is warranted. Limited tidal volume strategies reduce mortality in lung-injured patients, likely as a result of reduced overdistention and volutrauma. A large prospective clinical trial in human patients with ALI demonstrated that low tidal volume (6 ml/kg) ventilatory strategies reduced mortality rates by 22% compared with conventional tidal volumes of 12 ml/kg.[15]

One of the most common ventilator strategies for preventing atelectrauma is PEEP. Maintenance of expiratory pressures above the critical closing pressure (where alveolar collapse occurs) helps to maintain lung recruitment through all phases of the respiratory cycle and limit shearing injury.[16] An experimental study that compared equivalent tidal volume ventilation with and without PEEP demonstrated that PEEP helped to reduce the inflammatory response in the lungs.[14] To date, the use of high levels of PEEP to keep the lung open has not been shown to improve outcome in ARDS. A large prospective study showed no difference in outcome when low (8 cm H_2O) versus high (13 cm H_2O) levels of PEEP were used in humans with ARDS.[17]

Thus lung-protective ventilatory strategies focus on tidal volume reduction, with a goal of 6 ml/kg compared with traditional recommendations of 10 to 15 ml/kg, and limitation of peak airway pressures to the lowest value possible to maintain oxygenation, optimally below 30 to 35 cm H_2O (see Chapter 214, Advanced Mechanical Ventilation). Despite lack of clinical evidence, there is still a strong feeling that using PEEP to maintain alveolar recruitment throughout the ventilatory cycle is beneficial. One human clinical study, which used a variation of the aforementioned criteria, demonstrated a marked reduction in 28-day mortality and improved ability to wean patients from the ventilator in patients with ARDS.[18] Experimental studies suggest that manipulation of exhalation times, by altering respiratory rate[19] or inspiratory-to-expiratory ratios,[20] may provide an alternative method to maintain alveolar recruitment and avoid atelectrauma.

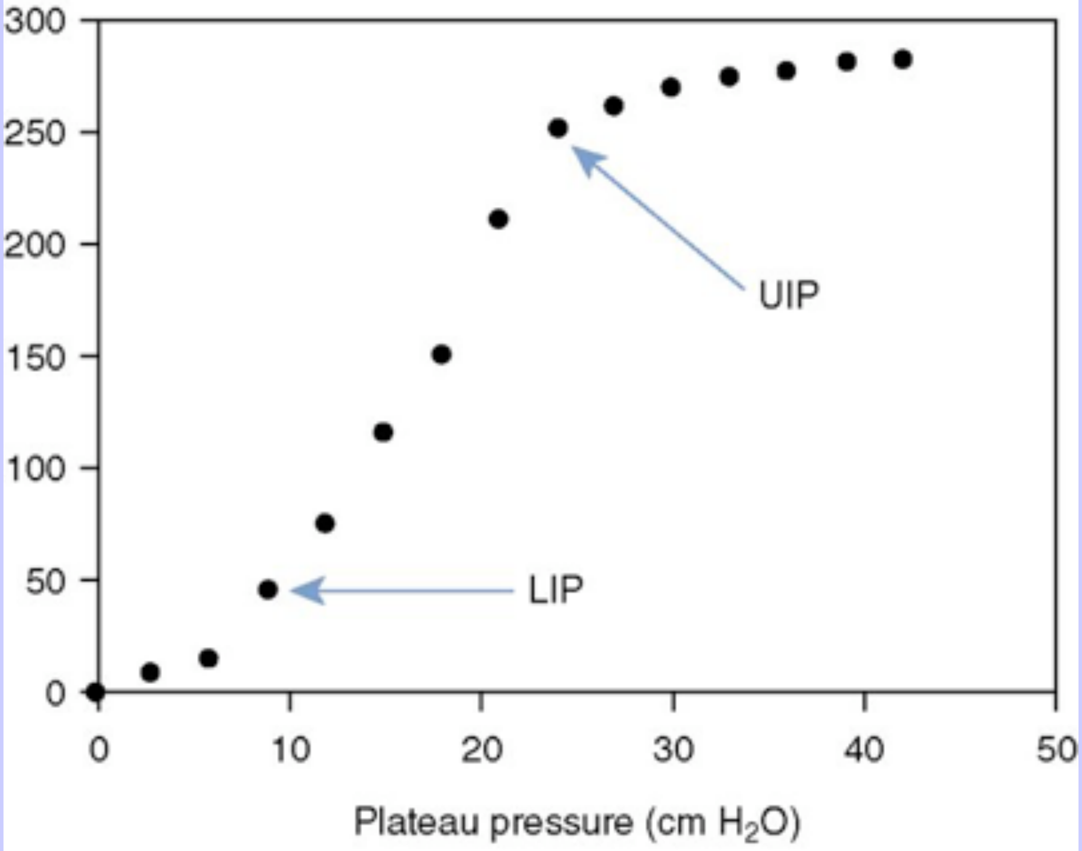
26.6 MONITORING TO REDUCE VALI

Barotrauma can be difficult to recognize initially in the ventilated patient. Auscultation of the thorax may reveal dull lung sounds. Palpation of the neck may reveal subcutaneous emphysema in cases with large-airway rupture; however, this finding will not be present when the rupture occurs within the alveoli. Cardiovascular instability, particularly tachycardia and hypotension, will occur when intrapleural pressure is sufficient to tamponade venous return to the heart. Hypoxemia and hypercarbia are late findings in patients with pneumothoraces. A spirometer that measures both inspiratory and expiratory tidal volumes may detect expiratory tidal volumes that are significantly lower than inspiratory tidal volumes, suggesting air leakage into the pleural space and pneumothorax.

Pulmonary function monitors that are inserted at the patient's airway and measure pressure and volume provide more reliable information about tidal volume delivery than do monitors located within the ventilator. This is because ventilator tubing compliance can lead to an overestimated tidal volume when measured at the ventilator. Depending on the mode of ventilation used, changes in pulmonary compliance will alter either tidal volume or peak airway pressures. For example, with pressure-controlled ventilation, changes in pulmonary compliance alter the tidal volume delivered for a ventilator breath; however, changes in compliance alter peak airway pressures with volume-controlled ventilation. With either mode of ventilation care should be taken to monitor serial changes in tidal volume and peak airway pressures to limit the risk for volutrauma and barotrauma.

Static pressure-volume (PV) curves have been recommended as a clinical tool to adjust ventilator settings to reduce the risk for VALI. Theoretically, PV curves provide valuable information about alveolar distention and recruitment, which should reduce the risk for both volutrauma and atelectrauma, respectively. Measurement of the PV curve involves incrementally increasing airway pressure over a wide range and measuring the tidal volume achieved for each step change (Figure 26-1). The upper inflection point on the inflation curve, denoted by limited changes in tidal volume despite continued increases in pressure, is thought to reflect the point above which overdistention and volutrauma occur. The lower inflection point on the inflation curve, denoted by the point at which a rapid increase in tidal volume occurs as pressure increases, is thought to reflect the pressure at which atelectatic lung is recruited. 21

Figure 26-1 A static pressure-volume curve. Airway pressure is incrementally increased over a wide range. At each pressure the resultant tidal volume is recorded. The lower inflection point represents the airway pressure at which increases result in linear increases in tidal volume. The upper inflection point represents the airway pressure at which increases in pressure no longer result in marked increases in tidal volume. *LIP,* Lower inflection point; *UIP,* upper inflection point.



The upper and lower inflection points on the PV curve may aid in setting peak airway pressure and tidal volume, and PEEP, respectively. However, these points should not be interpreted as precise pressures above or below which alveoli can be recruited. Controversy exists as to whether the upper and lower inflection points on the inflation curve accurately represent the points at which overdistention during inhalation and derecruitment during exhalation occur. Thus, newer recommendations include the use of incremental PEEP trials at set tidal volumes or determining the lower inflection point, or critical closing pressure, based on an exhalation PV curve to set optimal PEEP.[22,23] Use of the PV curve to select ventilator settings in a study of human patients with ARDS demonstrated reduced inflammatory mediators in bronchoalveolar lavage fluid, which may indicate reduced VALI, compared with control settings.[24] Despite the theoretic benefits, PV curves are used infrequently in many clinical human and veterinary patients because they are technically difficult to perform safely and their interpretation is not straightforward in many cases.

Direct monitoring of volutrauma and atelectrauma is technically difficult to impossible in the clinical patient. Tools that directly monitor overdistention (such as dynamic CT scanning) or cyclic recruitment of atelectasis (such as dynamic CT scanning, electrical impedance tomography, fast-responding intraarterial oxygen probes, and subpleural vital microscopy) have either limited clinical availability and financial limitations[25,26] or can be used only in the experimental setting.[19,27] Bedside techniques such as electrical impedance tomography may provide useful clinical tools for limiting VALI if they can be shown to help clinicians adjust ventilator settings in order to optimize alveolar recruitment while limiting cyclic collapse and overdistention. Additionally, the NICO machine (Novametrix Medical Systems Inc., Wallingford, CT) integrates airway flow and mainstream capnography to give the volume of carbon dioxide eliminated through the lungs per minute, also known as volumetric carbon dioxide. This measurement may be useful in determining optimal PEEP by detecting derangements in diffusion or ventilation that may occur secondary to overdistention, but the value can also be affected by changes in circulation, perfusion, or metabolism.[28] Further research in dogs is warranted.

26.7

SUGGESTED FURTHER READING*

VL Campbell, LG King: Pulmonary function, ventilator management, and outcome of dogs with thoracic trauma and pulmonary contusions: 10 cases (1994-1998). *J Am Vet Med Assoc*. **217**, 2000, 1505, *This retrospective study reports the outcomes of 10 dogs with pulmonary contusions following trauma who received mechanical ventilation as a supportive measure. A 30% survival to discharge was reported in this study*.

JA Lee, KJ Drobatz, MW Koch, et al.: Indications for and outcome of positive-pressure ventilation in cats: 53 cases (1993-2002). *J Am Vet Med Assoc*. **226**, 2005, 924, *This retrospective study evaluated mechanical ventilation in feline patients. It defines the reasons for positive-pressure ventilation in this population and details the ventilator strategies employed and outcomes obtained for cats in a veterinary intensive care unit.*

C Parent, LG King, TJ Van Winkle, et al.: Respiratory function and treatment in dogs with acute respiratory distress syndrome: 19 cases (1985-1993). *J Am Vet Med Assoc*. **208**, 1996, 1428, *This is one of the initial retrospective reports in veterinary medicine that describes ARDS in dogs. It reviews the treatment of these dogs and the role of mechanical ventilation in a subset of these patient and describes clinical outcomes.*

C Parent, LG King, LM Walker, et al.: Clinical and clinicopathologic findings in dogs with acute respiratory distress syndrome: 19 cases (1985-1993). *J Am Vet Med Assoc*. **208**, 1996, 1419, *This is the other initial retrospective report in veterinary medicine that describes ARDS in dogs and reviews the physical examination findings and diagnostic test results.*

* See the CD-ROM for a complete list of references.

27 Chapter 27 Pulmonary Thromboembolism

Lynelle R. Johnson, DVM, PhD, DACVIM

27.1 Box 27-1 Disorders Associated With Pulmonary Thromboembolism

- Immune-mediated hemolytic anemia
- Neoplasia
- Sepsis
- Protein-losing nephropathy and enteropathy
- Cardiac disease
- Hyperadrenocorticism
- Central catheter use
- Hemodialysis
- Total parenteral nutrition
- Hip replacement surgery
- Trauma

27.2 KEY POINTS

- Pulmonary thromboembolism (PTE) is a challenge to diagnose antemortem.
- PTE is a complication of diseases associated with hypercoagulability, endothelial damage, and stasis of blood flow.
- Identification of risk factors for PTE and disease associations is important for clinical recognition of this complication.
- Diagnostic results that can be used to support a diagnosis of PTE in a patient include positive D-dimer concentrations, echocardiographic detection of echogenic material in the pulmonary artery or evidence of acute right ventricular overload, and perfusion deficits on nuclear scintigraphy.
- Therapy for PTE includes management of the primary condition, support of oxygenation, and limitation of further growth of the clot with anticoagulants or thrombolytic agents.
- PROPHYLAXIS against thromboembolic complications should be considered in animals hospitalized with serious disease syndromes that have been associated with PTE.

27.3 INTRODUCTION

Obstruction of the pulmonary vascular bed can occur through blockage with fat, septic emboli, metastatic neoplasia, parasites (*Dirofilaria* or *Angiostrongylus*), or blood clots. It is likely that PTE results most commonly from formation of clot material (in the right side of the heart or at a distant site in the venous system) that breaks free and lodges in the pulmonary vasculature. Thrombosis in situ may also occur in association with pulmonary hypertension, heartworm disease, or other disorders of the pulmonary vasculature. PTE is likely as underdiagnosed in the veterinary population as it is in human medicine. Thrombi undergo 50% reduction in clot volume in the first 3 hours postmortem due to fibrinolytic dissolution; with heparin administration, clot volume is further reduced due to inhibition of further clot formation.[1] Thus necropsy confirmation of PTE can be difficult.

Antemortem clinical recognition of PTE is low because clinical signs and physical examination findings mimic those found in a variety of cardiopulmonary conditions. In an early report, PTE was a differential diagnosis for respiratory distress in less than 5% of dogs with PTE confirmed at necropsy.[2] In a more recent study,[3] PTE was suspected in 65% of dogs that had relevant respiratory signs and a recognized predisposing condition for thromboembolism, suggesting increased awareness of the condition. In dogs, immune-mediated hemolytic anemia, sepsis, neoplasia, amyloidosis, hyperadrenocorticism, and dilated cardiomyopathy are associated with increased risk for PTE, and neoplasia and cardiomyopathy are found most often in cats with PTE.[3,5]

As has been shown in human and veterinary studies, most veterinary cases have comorbid conditions complicating the primary clinical disease and potentially increasing the risk for thromboembolism. Because PTE is associated with nonspecific clinical symptoms such as tachypnea or difficulty breathing, knowledge of predisposing conditions (Box 27-1) is important for appropriate diagnosis and treatment.

27.4 PATHOPHYSIOLOGY

The key pathophysiologic responses to PTE include alterations in hemodynamics due to increased pulmonary vascular resistance, abnormalities in gas exchange, altered ventilatory control, and derangements in pulmonary mechanics. Rarely, pulmonary infarction contributes to the clinical picture. The pulmonary circulation is normally resistant to changes in blood flow that occur with vascular obstruction because distention of the elastic vasculature allows the pulmonary bed to accept the increase in flow from embolized regions without a change in pressure. However, vascular obstruction from embolization results in both physical obstruction and arterial vasoconstriction due to release of vasoactive mediators. The combination of these events causes a reduction in the cross-sectional area of the pulmonary circulatory bed and increased vascular resistance.

PTE results in hypoxemia primarily from ventilation–perfusion (V/Q) mismatch, although physiologic shunting and reduced diffusion capacity also contribute to reduced arterial oxygen content. Hypoxemia can be present with as little as 13% obstruction of the vascular bed in humans,[6] suggesting that even minor embolic disease is physiologically relevant. The severity of hypoxemia will be affected by underlying cardiopulmonary disease, reflex bronchoconstriction, and atelectasis. In the normal lung, most lung units have a V/Q ratio of 1; however, PTE causes a redistribution of blood flow, resulting in a wide spectrum of high, normal, and low V/Q units. Low V/Q units are the most important contributor to hypoxemia. As the degree of vascular obstruction exceeds 50% of the surface area of the circulatory bed, intrapulmonary shunting occurs, leading to venous admixture of blood and decreased oxygen responsiveness.[7]

Ventilation is controlled by the interaction between the sensors activated by elevated carbon dioxide in the central nervous system (CNS) and decreased partial pressure of arterial oxygen (PaO_2) in the periphery with the responders (respiratory muscles). PTE is associated with tachypnea and alveolar hyperventilation, although the mechanisms responsible for hyperventilation remain obscure. Platelet aggregation with release of humoral mediators and cytokines could activate C fibers and irritant receptors to effect breathlessness. Also, embolization of additional organs often occurs,[3,8] and obstruction of blood flow in the CNS could affect ventilatory control.

Changes in lung mechanics are likely important contributors to tachypnea, because increased resistance and decreased compliance greatly affect the work of breathing. Experimental studies in dogs have documented increased airway resistance following PTE; 5-hydroxytryptamine likely mediates this bronchoconstriction.[9] Lung compliance is reduced in patients with PTE because of pulmonary edema and atelectasis. Pulmonary edema appears to result from increased hydrostatic pressure associated with increased blood flow to nonembolized lung regions and from release of humoral factors that increase microvascular permeability.

27.5 HISTORY AND CLINICAL SIGNS

Historical features consistent with PTE included labored breathing, tachypnea, lethargy, and altered neurologic status. Additional clinical signs that may be observed include cough, syncope, and hemoptysis. Altered mental state is reported in 20% of human patients with PTE and may be related to transient hypoxemia or cerebral ischemia. In a report in dogs, abnormal neurologic status was recorded in over one third of affected animals[3] and thus may be a common finding with PTE. Importantly, obvious respiratory distress and tachypnea may be absent in some dogs or cats that have pulmonary embolization documented during necropsy.

Information regarding concurrent disease processes is essential to determine the risk of embolization for animals. In dogs with a variety of clinical syndromes leading to PTE, intravenous catheters had been placed in most, exogenous glucocorticoid excess was reported in half, use of cytotoxic agents was found in over one third, 21% had undergone recent surgical procedures, and 10% of dogs had been given blood transfusions.[3]

27.6 PHYSICAL EXAMINATION

Dogs with PTE typically demonstrate tachypnea or hyperpnea. Physical findings potentially consistent with PTE include labored breathing or tachypnea, tachycardia, and adventitious lung sounds (crackles or wheezes). Alternatively, lung and heart sounds may be damped because of pleural effusion. Cardiac murmurs are not uncommon in dogs or cats due to underlying cardiac pathology (particularly cardiomyopathy in cats) or pulmonary hypertension.

27.7 DIAGNOSTIC TESTING

The history of a disease association along with the acute onset of tachypnea and labored respirations is highly suspicious for pulmonary embolization; however, proving the presence of embolic disease antemortem is challenging. Routine laboratory work (complete blood count and chemistry profile) is submitted to investigate the underlying disease. Suspected risk factors for PTE identified in dogs with immune-mediated hemolytic anemia included high serum bilirubin levels, multiple intravenous catheters, and multiple blood transfusions.[4] Because urinary protein loss is a risk factor for PTE, a urinalysis is an essential part of routine screening. A urine protein-to-creatinine ratio over 0.5 is abnormal, and in animals with substantial urinary protein loss, an antithrombin level should be investigated. Concentrations less than 50% of 75% of normal are considered indicative of hypercoagulability and thus an increased risk for embolic complications.

Assessment of D-dimer concentration has been recommended to exclude PTE as a diagnosis when the test result is negative, or to increase the likelihood that embolization is present when a high titer is detected.[10] D-Dimer is a degradation product of fibrin that has undergone cross-linkage. It is more specific for fibrin formation than the standard fibrin degradation products test, which detects both fibrin and fibrinogen breakdown products. Unfortunately, many diseases in veterinary medicine result in elevation of D-dimer, and a negative test result does not exclusively rule out thromboembolism. A recent study in human medicine evaluating the accuracy of D-dimer testing versus location of embolus reported that a negative D-dimer result could be used to rule out most (93%) of large pulmonary emboli but only half of the subsegmental emboli.[11]

Arterial blood gas analysis generally reveals hypoxemia, hypocapnia, and a widened alveolar-arterial (A-a) gradient in most patients assessed. Calculation of the A-a gradient corrects for the contribution of alveolar hypoventilation to arterial hypoxemia but does not differentiate V/Q mismatch from other causes of hypoxemia. The A-a gradient is measured by the following formula using data obtained from an arterial blood gas.

$$(A - a) = PAO_2 - PaO_2$$

$$PAO_2 = \left[FiO_2 \left(P_b - P_{H_2O} \right) - PaCO_2 \middle/ RQ \right]$$

where FiO_2 = fraction of inspired oxygen, P_b = barometric pressure (760 mm Hg at sea level), PH_2O = water vapor pressure at a given body temperature (47 mm Hg), and RQ = respiratory quotient (0.8 to 1.0). The normal A-a is considered less than 10 to 15 mm Hg when the subject is breathing room air. Unfortunately the normal A-a in patients breathing supplemental oxygen cannot be defined accurately.

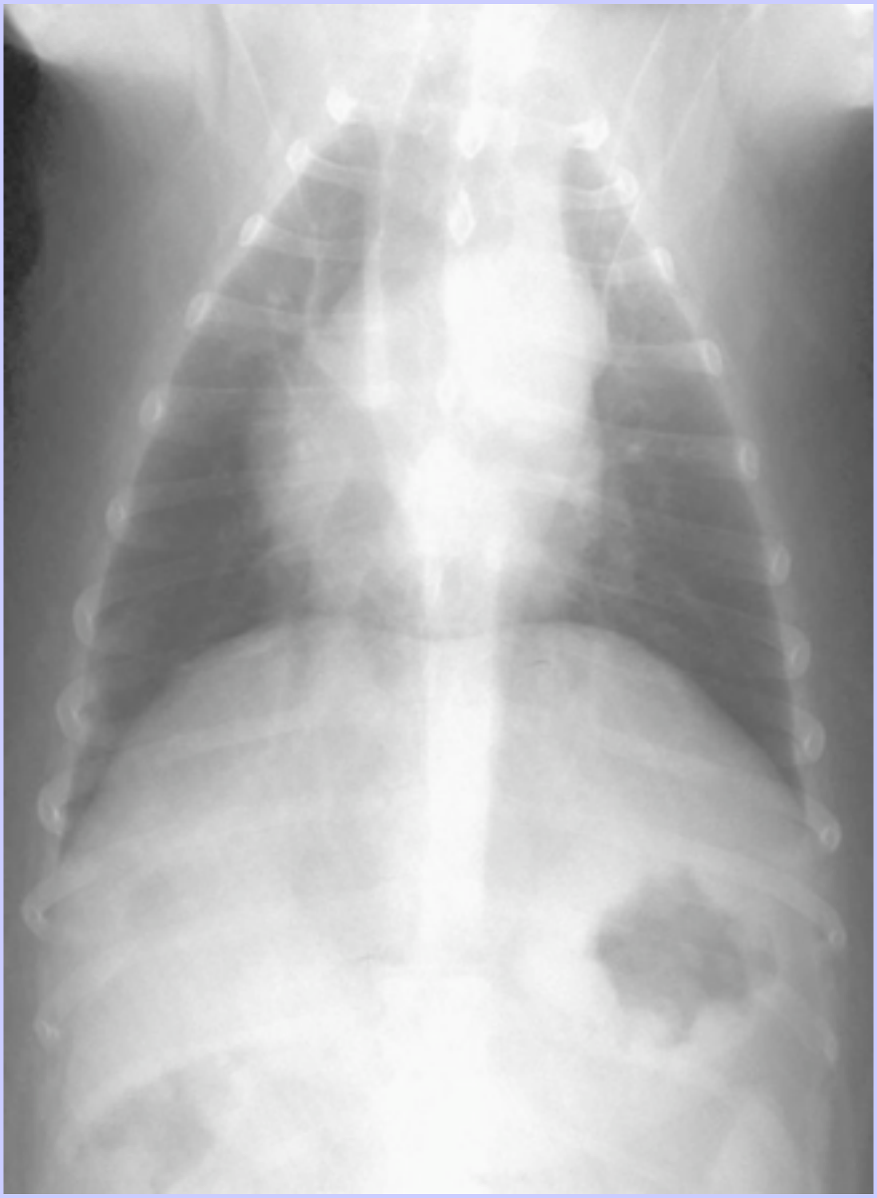
Arterial blood gas analysis during oxygen supplementation provides information on the potential mechanism underlying hypoxemia but does not help determine prognosis for recovery. A positive response to exogenous oxygen supplementation suggests that V/Q mismatching is the primary pathophysiologic event responsible for hypoxemia. A negative response suggests that intrapulmonary shunting or pulmonary infarction may be present.
Trends in oxygen responsiveness can be followed by calculating the oxygenation ratio (OR), also known as the PF 115
ratio, for PaO_2-to-FiO_2 ratio. This value is calculated by dividing the PaO_2 by the FiO_2. Normal values should 116
exceed 450 mm Hg.

Radiographs may help elucidate the underlying disease responsible for embolization or can reveal abnormalities associated with vascular obstruction (Figure 27-1). Previously reported thoracic radiographic abnormalities associated with PTE in dogs include pleural effusion, loss of definition of the pulmonary artery, alveolar infiltrates, cardiomegaly, hyperlucent lung regions, and enlargement of the main pulmonary artery.[12] Interstitial or alveolar infiltrates can represent focal or diffuse edema associated with overperfusion or atelectasis. Normal chest radiographic findings do not rule out the possibility of pulmonary thromboembolization, and normal findings in a patient with dramatic tachypnea and respiratory distress should be considered highly suspicious for PTE.[3]

Echocardiography can be considered a diagnostic modality for noninvasive assessment of the pulmonary vasculature. Clots occasionally can be seen in the right atrium or pulmonary arteries, or signs of acute right ventricular overload may be evident, such as right ventricular hypokinesis or dilation, abnormal septal motion, or tricuspid regurgitation. In human medicine, echocardiographic changes of right ventricular dilation, paradoxic septal motion, and increased velocity of tricuspid regurgitant jet are evident in most patients with clinically relevant pulmonary embolization.[13]

Definitive diagnosis of pulmonary embolization requires selective pulmonary angiography. Contrast angiography during computed tomography might also be employed; however, both techniques require anesthesia in veterinary patients. Nonselective pulmonary angiography can sometimes elucidate regions of absent vascular supply, but dilution of contrast medium can make this study difficult to interpret. V/Q scans have compared favorably with angiography for diagnosis of PTE in human and veterinary patients and are less invasive.[14] The utility of V/Q scans is limited in the veterinary clinical setting because the ventilation phase of the study is usually done under anesthesia to ensure adequate deposition of radioactive gas throughout the airways. Perfusion scanning, using technetium-labeled macroaggregated albumin, is a less invasive tool that can be performed without anesthesia. This diagnostic tool can reveal regions with absent radioactivity due to loss of pulmonary blood supply from embolization (Figure 27-2). In human medicine, a normal perfusion scan virtually excludes pulmonary embolization while an abnormal perfusion scan may reflect PTE or a variety of pulmonary conditions including pneumonia, atelectasis, edema, or contusions. The utility of perfusion scans for excluding PTE has not been evaluated in veterinary medicine.

Figure 27-1 Dorsoventral radiograph of the dog whose scan is displayed in Figure 27-2. Note the subtlety of the changes. The artery to the right caudal lung lobe appears to terminate abruptly at the eighth intercostal space. There is mild enlargement of the main pulmonary artery, but the cardiac silhouette is unremarkable. Lung fields are essentially unremarkable, with the exception of a focal area of interstitial opacity at the periphery of the right caudal lung lobe. (Courtesy Dr. Narelle Brown, University of California, Davis.)

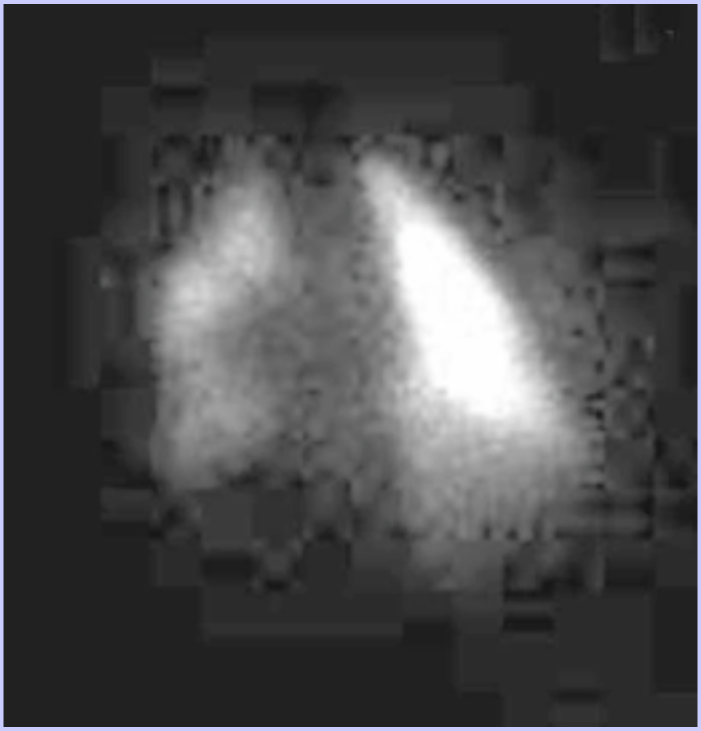


27.8 TREATMENT

Treatment and stabilization of the underlying condition should be initiated in order to limit further thrombus formation and subsequent embolization. Oxygen therapy is essential to reverse hypoxemia associated with V/Q mismatching and diffusion impairment. It is important to note that the degree of improvement in PaO_2 in response to exogenous oxygen supplementation will depend on the percentage of the vascular bed that is obstructed, the concentration of inspired oxygen administered, the distribution of V/Q mismatching across the lung, and the degree of shunting that is present.

Definitive therapy of pulmonary emboli through thrombolysis is possible but rarely is performed clinically because of the difficulty in establishing an antemortem diagnosis with conviction, as well as the side effects and costs of thrombolytic drugs. Primary drawbacks of thrombolytic therapy are induction of a hemorrhagic state and ischemia-reperfusion injury in the lung. Thrombolysis can be achieved with streptokinase, an enzyme that activates plasminogen conversion to plasmin. This drug has been used successfully for treatment of systemic embolization in the dog.[15] It is administered as an intravenous infusion at a loading dose of 90,000 U over 20 to 30 minutes, then 45,000 U over 3 to 7 hours. Clotting parameters must be followed throughout the course. Alternatively, tissue plasminogen activator can be used to cause direct fibrinolysis at the site of the clot. This drug directly activates plasmin within the clot and thus has fewer systemic side effects. Cost is substantial, and use of this drug has not been reported in animal pulmonary embolization.

Figure 27-2 Nuclear scintigraphy using technetium 99m–labeled macroaggregated albumin. This ventral view reveals a large perfusion deficit in the region of the right caudal lung lobe.



Anticoagulation with heparin and warfarin therapy can also be employed. Heparin therapy is instituted for 3 to 4 days before starting warfarin to avoid induction of a hypercoagulable state through inactivation of the natural anticoagulant, protein C, with warfarin therapy. Unfractionated heparin can be administered at 200 to 400 U/kg SC q6-8h to prolong activated partial thromboplastin time three-fold to four-fold. Alternatively, low-molecular-weight heparin preparations (enoxaparin, dalteparin) can be used. This class of drugs has more predictable pharmacokinetics in human medicine, and has enhanced factor Xa to IIa activity, which avoids the need for repeated testing of coagulation panels. Dosages are often extrapolated from human dosages. After heparinization, warfarin therapy can be started. Initial dosage recommendations are 0.5 mg per day in the cat or 0.1 mg/kg q24h in a dog. The goal of warfarin therapy is to prolong the one-stage prothrombin time (OSPT) to give an international normalized ratio (INR) of 2 to 3. The INR is calculated by:

$$\mathrm{INR} = (\text{patient OSPT} \;/\; \text{control OSPT})^{\mathrm{ISI}}$$

The ratio of patient-to-control OSPT is raised to the power of the ISI, the international sensitivity index of the thromboplastin in the kit used to determine the OSPT. This value is found in the instruction manual supplied by the kit manufacturer. Warfarin therapy is greatly complicated by individual differences in bioavailability, interference of metabolism by other drugs, the need for frequent monitoring of clotting times, and the risk of hemorrhage.

Newer platelet-inhibiting drugs such as clopidogrel and ticlopidine, which inhibit platelet aggregation, and fondaparinux, an inhibitor of thrombin, are under investigation for use in treatment or prevention of thromboembolism.

27.9 PROPHYLAXIS

In animals considered at risk for embolization, prophylaxis should be considered. Appropriate drugs that can be used include heparin, low-molecular-weight heparin, or aspirin; warfarin can also be used. Heparin can be administered at low dosages (75 to 100 U/kg SC q8h) that do not alter clotting times and thus do not require repeated monitoring. Aspirin must be dosed at a very low level to inhibit platelet production of thromboxane A_2 (a potent platelet aggregator) while maintaining endothelial production of prostacyclin (a vasodilator). In dogs a dosage of 0.5 mg/kg q12h is recommended, while in cats 25 mg/kg q72h has been suggested.

27.10 SUMMARY

Pulmonary thromboembolization is often a devastating consequence of an already serious illness. Treatment of the primary condition and supportive care during recanalization of the clot can be successful, however the possibility of further embolization exists. Prophylaxis for PTE should be considered in animals predisposed to embolic complications.

27.11 SUGGESTED FURTHER READING*

AP Carr, DL Panciera, L Kidd: Prognostic factors for mortality and thromboembolism in canine immune-mediated hemolytic anemia: a retrospective of 72 cases. *J Vet Intern Med.* **16**, 2002, 504, *Thromboembolic disease in any organ was found during necropsy in 20 of 25 dogs with immune-mediated hemolytic anemia, and the risk for thromboembolism was associated with elevated alkaline phosphatase, increased bilirubin, and decreased albumin levels.*

LR Johnson, MR Lappin, DC Baker: Pulmonary thromboembolism in 29 dogs: 1985-1995. *J Vet Intern Med*. **13**, 1999, 338, *This retrospective study of necropsy-confirmed pulmonary embolization established increased risk in dogs with immune-mediated hemolytic anemia, sepsis, and, neoplasia, and described results of blood gas analysis in affected dogs*.

PD Koblik, W Hornoff, SH Harnagel, et al.: A comparison of pulmonary angiography, digital subtraction angiography, and ^{99m}Tc-DTPA/MAA ventilation-perfusion scintigraphy for detection of experimental pulmonary emboli in the dog. *Vet Radiol Ultrasound*. **30**, 1989, 159, *Ventilation-perfusion scans compared favorably with angiography for diagnosis of PTE in this experimental model*.

OL Nelson, C Andreason: The utility of plasma d-dimer to identify thromboembolic disease in the dog. *J Vet Intern Med*. **17**, 2003, 830, *This prospective study found that D-dimer concentrations were highest in dogs with thromboembolic disease (affecting any organ system) when comparing clinically ill dogs and healthy dogs; however, a positive D-dimer concentration was of low specificity*.

CR Norris, SM Griffey, VF Samii: Pulmonary thromboembolism in cats: 29 cases (1987-1997). *J Am Vet Med Assoc*. **215**, 1999, 1650, *This retrospective study confirmed cardiac disease and neoplasia as the most common conditions underlying PTE in cats and reported frequent thoracic radiograph abnormalities that could be ascribed to pulmonary embolization*.

* See the CD-ROM for a complete list of references

28 Chapter 28 Smoke Inhalation

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28.1 KEY POINTS

- The lack of clinical veterinary information on smoke inhalation likely reflects a very high incidence of preadmission mortality. Hypoxia from carbon monoxide poisoning is presumed to be the most common cause of acute death.
- Direct thermal injury to the upper respiratory tract can cause laryngeal obstruction. Lower respiratory tract injury from irritant gases and superheated particulate matter can result in atelectasis, pulmonary edema, decreased lung compliance, and acute respiratory distress syndrome.
- Bacterial bronchopneumonia typically occurs later in the course of the condition and is usually secondary to therapeutic interventions or sepsis.
- Acute neurologic dysfunction may be seen initially or as a delayed syndrome.
- Significant dermal burn injury exacerbates morbidity and mortality.
- Aggressive oxygen supplementation is the immediate priority to hasten carbon monoxide elimination. Supportive measures for respiratory and neurologic complications follow.
- If carbon monoxide poisoning resolves, the prognosis is good in the absence of significant dermal burn injury, bronchopneumonia, or acute neurologic signs.

28.2 INTRODUCTION

A significant number of dogs and cats are likely to be involved in residential fires each year, yet there is very little information available regarding clinical cases. Most information is derived from experimental animal studies or extrapolated from the human literature. This dearth of clinical veterinary information is most likely due to a very high incidence of preadmission mortality.

28.3 PATHOPHYSIOLOGY

28.3.1 Carbon Monoxide

Carbon monoxide (see Chapter 87, Carbon Monoxide) is a nonirritant gas that competitively and reversibly binds to hemoglobin at the same sites as oxygen, with an affinity that is 230 to 270 times greater and results in marked anemic hypoxia.[1,2] It is produced by incomplete combustion of carbon-containing materials and is therefore most significant in enclosed fires as there is increasingly less oxygen available.[3] The resultant carboxyhemoglobin (COHb) also shifts the oxygen-hemoglobin dissociation curve to the left, resulting in less offloading at the tissue level.[1] There are three possible outcomes in pure, uncomplicated carbon monoxide poisoning: (1) complete recovery with possible transient hearing loss but no permanent effects, (2) recovery with permanent central nervous system abnormalities, and (3) death.[1,4-8] Carbon monoxide poisoning is the main cause of acute death from smoke inhalation in humans, and death is due to cerebral and myocardial hypoxia.[5,6]

28.3.2 Hydrogen Cyanide

Hydrogen cyanide (HCN) (see Chapter 86, Cyanide) is most prevalent in fires involving wools, silks, and synthetic nitrogen–containing polymers (e.g., urethanes, nylon). It is a nonirritant gas that interferes with the utilization of oxygen by cellular cytochrome oxidase, thereby causing histotoxic hypoxia.[2,5] The incidence and significance of cyanide toxicity in veterinary smoke inhalation victims remain undefined.[3,9]

28.3.3 Thermal Injury

Direct thermal injury involving hot, dry air is highly unusual distal to the larynx because heat is dissipated effectively by the thermal regulatory system of the nasal and oropharyngeal areas.[10,11] Thermal injury can manifest as mucosal edema, erosions, and ulceration. Of greatest concern is the potential for laryngeal edema that may result in fatal upper respiratory tract obstruction. Although these changes may not be apparent initially, they can be progressive. In one study, a tracheostomy was required for laryngeal obstruction in 2 of 27 dogs and was performed 24 and 72 hours after admission.[7] Steam has a much greater heat capacity than dry air and is therefore liable to produce more extensive injury throughout the respiratory tract.[10] Inhalation of superheated particulate matter (mainly soot) can result in thermal injury to the trachea and lower respiratory tract.

28.3.4 Irritant Gases and Superheated Particulate Matter

A variety of irritant noxious gases can be inhaled during a fire, depending on the nature of the materials undergoing combustion. These include short-chain aldehydes, gases that are converted into acids in the respiratory tract (e.g., oxides of sulfur and nitrogen), highly water-soluble gases (e.g., ammonia, hydrogen chloride), and benzene (from plastics).[5,11] Particulate matter acts as a vehicle by which these gases can be carried deep into the respiratory tract. The pathophysiology that results depends on the types of gases and particulate matter inhaled, the duration of exposure, and underlying host characteristics.[10,12]

28.3.4.1 Reduced Lung Compliance

Lung compliance may be markedly reduced as a result of alveolar atelectasis and pulmonary edema. Alveolar atelectasis can occur within seconds of injury due to impaired pulmonary surfactant activity (see Chapter 29, Atelectasis).[2,13,14] Pulmonary edema results from increased permeability of the microvasculature, possibly associated with sequestered leukocytes (see Chapter 21, Pulmonary Edema).[14,15] Alveolar edema is exacerbated by a concurrent increase in epithelial permeability.[15] Pulmonary edema can occur within minutes of smoke inhalation, although it typically develops over a period of up to 24 hours.[10] Ventilation-perfusion alterations also occur, and acute lung injury and acute respiratory distress syndrome are potential sequelae (see Chapter 24, Acute Lung Injury and Acute Respiratory Distress Syndrome).

28.3.4.2

Airway Damage and Obstruction

The mucociliary escalator is significantly impaired following smoke inhalation. Progressive mucosal edema may be accompanied by mucosal sloughing over several hours and the damaged epithelium gives rise to pseudomembranous casts.[10,14] Marked tracheobronchitis, necrotizing bronchiolitis, alveolar hyaline membrane formation, and intraalveolar hemorrhage may all follow.[10,14] Smoke inhalation induces a reflex bronchoconstriction, and airway obstruction is exacerbated by the copious secretions and edema fluid.[10]

28.3.4.3

Bacterial Pneumonia

Smoke inhalation may increase the likelihood of bacterial pneumonia by impairment of alveolar macrophage function. In addition, the stagnant luminal contents create a milieu conducive to bacterial colonization. Nevertheless, bacterial pneumonia is thought to typically occur as a secondary phenomenon following therapeutic interventions such as endotracheal intubation and tracheostomy, or due to sepsis associated with dermal burn injuries.[12,16] Infection usually is not seen for at least 12 to 24 hours and is associated with a higher incidence of respiratory failure. [10,12,16] *Pseudomonas aeruginosa, Staphylococcus* spp, and *Streptococcus* spp are most commonly involved in humans, but it is unknown if the same is true of dogs and cats.

28.3.5

Dermal Burn Injury

The morbidity and mortality associated with smoke inhalation are much greater when significant concurrent dermal burn injury is present.[7,9,11] This is due to both the pulmonary pathophysiology (pulmonary edema, bacterial pneumonia, acute lung injury, and acute respiratory distress syndrome) associated with dermal burns and their management requirements, including more aggressive fluid therapy and repeated general anesthesia (see Chapter 158, Thermal Burn Injury).[9,11]

28.4

HISTORY

If owner contact is possible, a full medical history should be obtained at the appropriate time. The history of current illness is usually related to being involved in an enclosed-space fire, and the duration of exposure and types of items involved should be ascertained. The patient's neurologic status at the scene predominantly reflects the degree of carbon monoxide poisoning. Paroxysmal or intractable coughing may suggest the inhalation of more irritating gases.

28.5

PHYSICAL EXAMINATION

Physical examination findings depend on a number of factors including the type, severity, and duration of smoke inhalation; the presence of dermal burn injuries; oxygen supplementation by human paramedics; delay in arrival at the hospital; and the patient's preexisting health status.

Neurologic abnormalities on admission may include reduced mental status, from depression through to coma, as well as anxiety, agitation, ataxia, and the developement of convulsions. New neurologic signs have been reported after 2 to 6 days in dogs that had neurologic dysfunction initially.[17,18] Lethargy may be a common finding in cats.[19]

Respiratory signs may be absent initially and can take 24 hours or more to develop; however, two studies found that animals without respiratory abnormalities at admission typically did not go on to develop any significant problems.[7,14,19] Clinical signs include tachypnea, panting (dogs), open-mouth breathing, dyspnea, inspiratory stridor, increased tracheal noise, harsh lung sounds, expiratory wheezes, and nasal discharge.[5,7,10,15]

Cardiovascular findings may or may not be normal and depend on both the myocardial effects of carbon monoxide and HCN toxicity and the coexistence of significant dermal burn injury. Cardiovascular status tends to normalize quickly in uncomplicated cases, but complicated cases are more likely to have a range of cardiovascular abnormalities that persist for a longer period.[10,12,19] The cherry red appearance of mucous membranes (and skin) attributed to carboxyhemoglobinemia is rarely witnessed in clinical cases. This probably represents a high level of preadmission mortality in patients that would fall into this category.[6] Individuals that live long enough to be treated are more likely to have either normal or hyperemic mucous membranes. Hyperemia may be due to carboxyhemoglobinemia, cyanide toxicosis, systemic vasodilation, and local vasodilation due to mucosal irritation, and this may mask both concurrent perfusion abnormalities and cyanosis.[7]

The animal's coat is likely to smell of smoke. Ptyalism may be present and there may be evidence of soot in the oral cavity (or on microscopic examination of saliva). Mucosal edema and burns inside the oral cavity as well as on the face and lips may suggest smoke inhalation injury to the respiratory tract, but such findings can carry a high incidence of false positives in humans.[14] In two retrospective veterinary studies, only 1 of the 27 dogs and none of the 22 cats had a major dermal burn injury; minor injuries such as singed hair and skin lacerations were more common in dogs.[7,19] Evidence of ocular irritation, including conjunctival hyperemia, blepharospasm, corneal lesions, and ocular discharge, may be present.

28.6 CLINICAL EVALUATION

28.6.1 Arterial Blood Gas Analysis

Initially, when carbon monoxide (and HCN) poisoning is likely to be the predominant cause of morbidity, arterial partial pressure of oxygen (PaO_2) may remain within normal limits (see Chapter 87, Carbon Monoxide).[1,2,10] Oxygen saturation, based on pulse oximetry, may also appear normal because these devices do not differentiate between COHb and oxyhemoglobin.[3] Co-oximetry allows direct measurement of oxyhemoglobin and COHb (see Chapter 208, Blood Gas and Oximetry Monitoring).[9] A reduction in the arterial-venous oxygen gradient may be suggestive of significant HCN toxicity.[9,20] Repeated arterial blood gas analysis is invaluable in the detection and monitoring of the potentially progressive respiratory complications of smoke inhalation. Hypoxemia, hypercarbia, and an increased alveolar-arterial oxygen gradient may be present. In one retrospective study of 14 dogs the PaO_2-to-FiO_2 (inspired oxygen concentration) ratio had a nadir at 32 hours postadmission (median value 269); this seemed to correlate with the worst clinical respiratory signs.[7]

28.6.2 Acid-Base Status

Acidosis is likely and may be of respiratory, metabolic, or mixed origin.[10-12] Hyperlactatemia may be present as a result of tissue hypoxia, and excessively high plasma lactate levels at admission are a sensitive indicator of HCN intoxication (independent of hypoxemia) in humans.[20]

28.6.3 Thoracic Radiography

Thoracic radiographic abnormalities may be absent initially but usually appear within the first 24 hours and can be expected in 70% to 80% of affected dogs and cats.* Radiographic changes do not always correlate with either the severity of respiratory tract injury or with patient morbidity.[7,10,15,19] An asymmetric radiographic pattern consistent with pulmonary edema is typical with alveolar, interstitial, and peribronchial changes.[7,15,19,21] Diffuse coalescing consolidation, collapse of the right middle lung lobe, and pleural effusion (especially in cats) have all been reported.[7,10,19,22] If bacterial pneumonia develops, a more pronounced alveolar pattern with air bronchograms can be expected.[15]

* References 3, 7, 9, 10, 19, 21.

28.6.4 Laryngoscopy, Bronchoscopy, and Transtracheal Aspiration

Laryngoscopy is useful in sedated or unconscious animals to detect potentially progressive laryngeal obstruction. Fiberoptic bronchoscopy is used widely in humans to examine the lower airway. Carbonaceous particulate matter in the airway confirms the diagnosis and direct visualization of the anatomic level, and extent of airway injury is possible along with sample collection.[3] Serial examinations may need to be performed as respiratory changes progress.[9] General anesthesia is required in veterinary patients in the absence of a tracheostomy, so a risk-benefit assessment must therefore be made in considering this procedure. Transtracheal aspiration may be used in veterinary patients. Samples may reveal carbonaceous particulate matter as well as cytologic changes consistent with thermal injury affecting the ciliated epithelial cells in particular.[23] This technique is also useful for the diagnosis of bacterial bronchopneumonia and in obtaining samples for culture and sensitivity testing.

28.7 DIAGNOSIS

Smoke inhalation is suspected in cases with a history of involvement in an enclosed-space fire along with facial burns, especially if carbonaceous particulate matter is present in the oral cavity or on microscopic examination of saliva. The results of physical examination and clinical evaluation support the diagnosis. In animals with significant dermal burn injury, and in the absence of a COHb measurement, the use of a transtracheal wash or bronchoscopy may be necessary to diagnose smoke inhalation as the cause of respiratory abnormalities.

28.8 TREATMENT

On the basis of the history and the initial findings of physical examination and clinical evaluation, smoke inhalation victims can be divided broadly into the following groups: (1) those that are without clinical signs and assessed to be at low risk of progression, (2) those with mild signs but assessed to be at high risk of progression, and (3) those that require intensive treatment from the outset.[3] Treatment of smoke inhalation must be tailored to this initial assessment and adapted thereafter based on regular patient evaluation.

28.8.1

Oxygen Supplementation

Oxygen supplementation is the immediate priority for a patient with presumed carbon monoxide toxicity and may cause significant clinical improvement within minutes.[7,16,18] The half-life of carbon monoxide is approximately 250 minutes in patients with normal respiratory exchange on room air, but is reduced to 26 to 148 minutes with an FiO_2 of 100%.[5,24] The use of hyperbaric oxygen therapy has been reported in humans, but providing an FiO_2 of 100% via endotracheal intubation is an effective, readily available alternative that allows access to the patient. Treatment periods ranging from 30 minutes up to 6 hours have been described.[10,25,26] Oxygen supplementation clearly has a crucial therapeutic role in the respiratory complications that may develop subsequently.

28.8.2

Cyanide Toxicity

Treatment for cyanide toxicity involves intravenous sodium nitrite followed by intravenous sodium thiosulfate (see Chapter 86, Cyanide). However, sodium nitrite may not be appropriate in smoke inhalation victims because it results in the formation of methemoglobin and will further compromise oxygen-carrying capacity.[5] Sodium thiosulfate should therefore be used alone.

28.8.3

Airway Management

A tracheostomy may be required to treat laryngeal obstruction. Given the potentially disastrous effects of bacterial pneumonia in these patients, strict aseptic technique must be maintained during the procedure, with regular suctioning and humidification thereafter. The empiric use of bronchodilators is indicated, especially in patients with wheezes on auscultation. Options include terbutaline (0.01 mg/kg IV or IM in both dogs and cats), aminophylline (dogs: 10 mg/kg slowly IV [diluted], cats: 4 mg/kg slowly IV [diluted]); and inhaled albuterol. Supplemental oxygen must be humidified and regular saline nebulization followed by coupage should also be 120
performed. Human clinical studies have suggested that coupage is contraindicated in the presence of bacterial 121
pneumonia (see Chapter 23, Aspiration Pneumonitis and Pneumonia). Gentle activity is to be encouraged if possible, and mucolytics such as bromhexine and acetylcysteine may also be helpful. Antitussives are best avoided because they will reduce airway clearance.

28.8.4

Sedation

Animals that are agitated at initial contact may be exhibiting neurologic symptoms associated with carbon monoxide (and HCN) toxicity. Appropriate chemical restraint to allow more aggressive oxygen supplementation is empirically justified in such cases. Thereafter, sedation may be required to minimize anxiety associated with dyspnea. Low-dosage opioids may be adequate, and additional sedation (e.g., acepromazine) may be necessary, especially in patients with upper respiratory tract compromise (see Chapter 162, Sedation of the Critically Ill Patient).

28.8.5 Mechanical Ventilation

Assisted ventilation may be required either due to inadequate spontaneous ventilation or respiratory failure (see Chapter 213, Basic Mechanical Ventilation).[9] Positive end-expiratory pressure is beneficial in patients with atelectasis.[9,13] Continuous positive airway pressure, provided to spontaneously breathing patients, may be an alternative in the absence of hypoventilation, but this will usually necessitate orotracheal intubation or tracheostomy.[27,28]

28.8.6 Intravenous Fluid Therapy

Smoke inhalation victims may require only maintenance fluid therapy; however, fluid requirements are significantly increased in those with dermal burn injury (see Chapter 158, Thermal Burn Injury). Although a number of experimental studies have demonstrated an increase in extravascular lung water following aggressive intravenous fluid therapy in smoke inhalation victims, there appears to be no consensus regarding the clinical relevance of this finding.[9,14,29] Pulmonary pathology in smoke inhalation certainly justifies caution with fluid therapy, but excessive fluid restriction has been associated with increased morbidity and a “conservatively aggressive” approach with close monitoring may be rational.[30]

28.8.7 Additional Therapies

Prophylactic antibiotics are not recommended due to the risk of selecting for resistant organisms. In animals with suspected bacterial pneumonia, antibiotic selection should be based on culture and sensitivity testing of samples collected by transtracheal wash or bronchoscopy. Gram stain examination of these samples can guide drug selection while results are awaited. Otherwise broad-spectrum coverage for both gram-negative and gram-positive infections should be instituted and then amended if necessary once the results are obtained. Blood cultures are recommended in animals that are thought to have developed bacterial pneumonia due to sepsis.[3]

The use of glucocorticoids following smoke inhalation has been widely studied. Experimental studies report variable effects associated with this treatment, but the vast majority of clinical reports point to an increased incidence of bacterial pneumonia with no clear clinical benefit.[3,7,11,14,31] The use of glucocorticoids is therefore not recommended in these patients.[3,9,14]

The permeability edema following smoke inhalation was said to be less responsive to standard diuretic therapy than high-pressure edema. However there is more recent evidence in support of multimodal beneficial effects of furosemide administration in such cases (see Chapter 21, Pulmonary Edema). Empiric diuresis should be avoided in hypovolemic or dehydrated patients.

28.9 PROGNOSIS

Mortality rates in people following admission for smoke inhalation have been reported as less than 10% without and 25% to 65% with dermal burn injury.[9] Of the 27 dogs in one retrospective canine study, 4 died and a further 4 were euthanized. In uncomplicated cases, dogs recovering from the initial carbon monoxide poisoning had a favorable prognosis, with improvements in respiratory signs over 24 hours. However, dogs that were clinically worse the following day were more likely to die, be euthanized, or require prolonged hospitalization.[7] In another study, dogs admitted with acute neurologic signs had an overall mortality rate of 46%.[17] Despite initial improvement, acute, delayed neurologic signs developed in 46% of the dogs within 2 to 6 days. Mortality rate for this group was 60%.[17] None of the 22 cats in a retrospective feline study died, but 2 were euthanized for severe respiratory or neurologic signs.[19] Animals with concurrent dermal burn injury should be given a more guarded prognosis from the outset. Although smoke inhalation can result in permanent changes to lung structure, any long-term effects on lung function are unlikely to be clinically significant.[3,7,9,15]

28.10 SUGGESTED FURTHER READING*

KJ Drobatz, LM Walker, JC Hendricks: Smoke exposure in dogs: 27 cases (1988–1997). *J Am Vet Med Assoc*. **215**, 1999, 1306, *To the authors' knowledge this is the only sizeable clinical canine retrospective study to have been published to date. As such it is invaluable, because it allows a comparison between actual clinical data and information derived from animal experiments or extrapolated from humans.*

KJ Drobatz, LM Walker, JC Hendricks: Smoke exposure in cats: 22 cases (1986–1997). *J Am Vet Med Assoc*. **215**, 1999, 1312, *To the authors' knowledge this is the only sizeable clinical feline retrospective study to have been published to date. As such it is invaluable because it allows a comparison between actual clinical data and information derived from animal experiments or extrapolated from humans.*

CS Farrow: Inhalation injury. In RW Kirk (Ed.): *Current veterinary therapy VIII*. 1983, Saunders, Philadelphia, *This chapter provides Farrow's classification scheme with appropriate management for smoke inhalation injury. It provides useful clinical information and is a must read (although it recommends the use of methylprednisolone).*

CB Jackson, KJ Drobatz: Neurologic dysfunction associated with smoke exposure in dogs. *J Vet Emerg Crit Care*. **12**, 2002, 193, *This abstract of a retrospective canine study provides invaluable clinical data. The case population overlaps with that in reference 7.*

TR Tams, RG Sherding: Smoke inhalation injury. *Compend Contin Educ*. **3**, 1981, 986, *This is one of only a few veterinary review articles on smoke inhalation injury currently available and as such is a must read. It is thorough and well presented.*

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* See the CD-ROM for a complete list of references

29 Chapter 29 Atelectasis

Janet Aldrich, DVM, DACVECC

29.1 KEY POINTS

- Atelectasis is an important cause of hypoxemia in critically ill patients.
- The three major mechanisms causing atelectasis are compression, oxygen absorption, and depletion of surfactant.
- Critically ill patients are at risk for atelectasis because they are often recumbent, receive high inspired oxygen levels, and can have decreased lung expansion.
- A multimodal approach to respiratory care includes techniques to minimize atelectasis.

29.2 INTRODUCTION

Atelectasis is an airless or partly airless state of the lung that leads to alveolar collapse.[1] Diagnosis of atelectasis is important because it is a potentially reversible cause of severe hypoxemia, and management protocols to decrease its risk and to reexpand the lung are available.

29.3 PATHOPHYSIOLOGY

29.3.1 Factors Preventing Alveolar Collapse

Alveoli and small airways are extremely delicate structures with no distending properties of their own. Ultimately the size of a given alveolus will depend on the balance between the coexisting collapsing and distending forces to which it is subjected. The primary collapsing force is surface tension, and this is opposed by four main distending forces: (1) transpulmonary pressure, (2) the tethering effect of surrounding structures, (3) surfactant, and (4) the gaseous nitrogen skeleton.[2,3] When the collapsing forces outweigh the distending forces alveoli and small airways will collapse, producing atelectasis. Due to their inherent stability issues, alveoli and small airways are in one of three states: (1) fully open, (2) open but smaller than normal (hypoventilated), or (3) collapsed. Atelectasis creates areas of lung that are perfused but not ventilated (no ventilation-perfusion [V/Q] regions) so they can no longer participate in gas exchange. Unlike that of low-V/Q regions, this mechanism of hypoxemia will not improve with oxygen therapy.

29.3.2 Atelectasis

Compression, airway obstruction, inadequate lung expansion, alveolar fluid accumulation, and alveolar trauma are all well-recognized causes of atelectasis. Airway obstruction and hypoventilation predispose to atelectasis secondary to absorption. Compression of lung tissue forces air out of alveoli to cause collapse, and fluid accumulation within alveoli increases the surface tension forces and may also result in atelectasis. Alveolar trauma can lead to fluid exudation into alveoli and loss of surfactant, increasing the likelihood of collapse. Shear forces generated during cyclic alveolar collapse and reexpansion constitute a mechanism of ventilator-induced lung injury that creates alveolar trauma and atelectasis.[3] Alveolar surfactant production is dependent on an adequate alveolar blood supply. When pulmonary perfusion is compromised, such as following pulmonary embolism, inadequate surfactant production can occur and may lead to atelectasis.

29.3.3 Absorption Atelectasis

Gases trapped distal to a closed airway are reabsorbed into the pulmonary circulation because the partial pressure of gases in end-capillary mixed venous blood is lower than in the alveoli, thus establishing a gradient for reabsorption. The alveolus eventually becomes airless and collapses. Air contains nitrogen, which is poorly soluble and absorbed more slowly than highly soluble oxygen. Hence nitrogen provides support for the alveolus preventing collapse (a “nitrogen skeleton”) and may persist in the alveolus for hours to days. Absorption atelectasis occurs far more rapidly in patients breathing enriched oxygen mixtures because the nitrogen skeleton is diminished or absent.[2] In situations of airway obstruction, atelectasis may be mitigated by entry of gas from adjacent lobules. Respiratory bronchioles and alveolar ducts anastomose between adjacent lung segments in dogs and are the most likely primary site of collateral ventilation in this species.[4] In patients breathing high oxygen concentrations, hypoventilated alveoli may also fall victim to absorption atelectasis when the rate of gas leaving alveoli and entering the pulmonary blood exceeds the degree of ventilation.

29.3.4 Atelectasis Without Volume Loss

Classically atelectasis is associated with a loss of lung volume, and this is often used as an aid in its radiographic diagnosis. Atelectasis may, however, be associated with edema or infiltration of inflammatory cells into the collapsed alveoli and airways, thus creating a condition of airlessness without volume loss.

29.4 CAUSES OF ATELECTASIS

29.4.1 Inadequate Lung Expansion

Weakness of respiratory muscles, pain, and centrally mediated respiratory depression can cause inadequate lung expansion and atelectasis. This atelectasis will occur predominantly in the dependent regions of the lung where transpulmonary pressure is smallest at functional residual capacity (FRC). Recumbent, larger animals are particularly prone to this dependent collapse. Atelectasis as a result of inadequate lung expansion can also occur with positive-pressure ventilation strategies that include low end-expiratory volume, which may be used in an effort to avoid volutrauma.[5]

29.4.2 Extramural Airway Compression

Airway compression can result from parenchymal and extraparenchymal masses; pleural space disease with accumulation of air, fluid, or intrusion of abdominal contents; or chest wall disease (flail chest) that allows the underlying lung to collapse.

29.4.3 Intraluminal and Mural Obstruction

As described previously, airway obstruction can contribute to absorption atelectasis. Intraluminal obstruction may be caused by foreign bodies or excessive accumulation of secretions. Mural lesions include loss of structural integrity of the cartilaginous airways and proliferative lesions that protrude into the airway. Bronchoconstriction may narrow airway diameter enough to cause obstruction.

29.4.4 Anatomic Predisposition

Segments of lung with a high ratio of pleural surface-to-volume may be more prone to atelectasis after airway obstruction. In these segments, high resistance to collateral flow limits collateral ventilation. Based on these characteristics, the right middle lung lobe and the left upper lobe in dogs were predicted to be more likely to develop atelectasis following airway obstruction.[4]

29.4.5 Anesthesia

Numerous factors that are associated with general anesthesia may increase the likelihood of atelectasis. These include inadequate lung expansion, high inspired oxygen concentrations, and endobronchial intubation. During anesthesia, reduction in chest wall movement and relaxation of the diaphragm allowing its anterior displacement contribute to reduction in lung volume (decreased FRC) and small airway closure in the dependent lung.[6] In healthy, spontaneously breathing dogs anesthetized for orthopedic procedures, atelectasis caused static respiratory compliance to decline progressively.[7] In addition, anesthetic agents are almost universally respiratory depressant in nature, which may further contribute to poor lung expansion. Anesthetized patients are also at risk of absorption atelectasis as a consequence of breathing high concentrations of oxygen. As mentioned previously, this is a particular problem in poorly ventilated regions of the lung.

Endobronchial intubation will result in ventilation of only one lung, and without ventilation the other lung will soon become atelectatic. Endotracheal tubes move caudally and cranially with flexion and extension of the head and neck. Therefore an endotracheal tube may move into and out of the mainstem bronchus if it is positioned too close to this area.[6] Atelectasis of the obstructed, unventilated lung will be accelerated by breathing high oxygen concentrations.

29.4.6 Other Mechanisms

Atelectasis secondary to prolonged recumbency occurs commonly in critically ill patients. Contributing factors include inadequate lung expansion because of positioning, pain, drugs, or concurrent disease, and high inspired oxygen concentrations. Pulmonary thromboembolism may cause edema and atelectasis because of depletion of surfactant as a result of decreased delivery of the components of surfactant production.[8] Chest physiotherapy with either hand clapping or a mechanical percussor in anesthetized, paralyzed, ventilated dogs may cause atelectasis, and thoracic compression by elastic bandaging can reduce lung volume below FRC, also predisposing to atelectasis.[9] Massive pulmonary collapse has been reported as an infrequent complication of asthma in human patients; it has not been reported to date in veterinary patients.[10] Improper technique in suctioning an endotracheal tube can also cause atelectasis. Suction catheters that are too large and occlude the endotracheal tube prevent entraining of room air and can cause excessive reduction in airway pressure and small airway and alveolar collapse.

29.5 CONSEQUENCES OF ATELECTASIS

29.5.1 Hypoxemia

Airway obstruction decreases ventilation relative to perfusion (low V/Q) or completely obstructs airflow (no V/Q, shunt) in a lung that is still perfused. The blood leaving that unit is not adequately oxygenated and contributes to venous admixture and hypoxemia. Hypoxemia as a consequence of no-V/Q regions is not responsive to oxygen therapy. In the normal lung the severity of hypoxemia due to atelectasis may be attenuated by hypoxic pulmonary vasoconstriction. This pulmonary vascular reflex decreases blood flow to poorly ventilated alveoli, improving V/Q matching and decreasing venous admixture. Hypoxic pulmonary vasoconstriction is decreased by acidemia, increased cardiac output, and severe systemic hypoxemia but was shown to be stable for 4 hours in experimental dogs without these complications.[11]

29.5.2 Prolonged Atelectasis

Pulmonary function can be restored to regions of collapsed lung despite prolonged periods of atelectasis. In experimental dogs, complete obstruction of a bronchus was created for periods ranging from 5 weeks to 10 months after which the patency of the bronchus was reestablished. Biopsy specimens were obtained at various intervals. The atelectatic lobes were small, with a liver-like appearance and rubbery consistency. Reexpansion resulted in a nearly normal histologic appearance.[12]

29.5.3 Reexpansion Pulmonary Edema

Pulmonary edema may follow rapid expansion of areas of the lung that have been collapsed for several days or more and is more likely to occur when negative pressure is applied manually to the chest tube than with more passive techniques of reexpansion.[13] Reexpansion pulmonary edema is associated with an increase in cytokines and in the inflammatory response, both in the reexpanded and in the contralateral lung.[14] Gradual reexpansion is recommended when treating prolonged atelectasis.

29.6 CLINICAL SIGNS

29.6.1 History and Physical Examination

Prolonged recumbency, high inspired oxygen concentrations, and recent anesthesia are associated with atelectasis.

Clinical signs include tachypnea, dyspnea, and cyanosis. The most notable change in thoracic auscultation is a decrease in breath sound intensity over the affected area. Wheezes (musical, monophonic, or polyphonic breath sounds) suggest a significant flow obstruction, but the correlation between airway obstruction and detectable wheezing is variable. Crackles (discontinuous breath sounds) occur when airways previously closed snap open. They may be present in small airway and alveolar collapse.[15] Fever has been reported in humans and experimental dogs with atelectasis.[16] In a rat model of atelectasis, alveolar macrophages produced increased interleukin-1 and tumor necrosis factor, and these were thought to be responsible for the fever.[17]

29.7 DIAGNOSTIC TESTS

29.7.1 Blood Gas Analysis

Atelectasis may cause hypoxemia of a magnitude that will correlate with the degree of shunt present.[5] This is a non-specific finding as atelectasis is only one of many causes of hypoxemia. Chapters 9 and 15, Tachypnea and Hypoxemia and Respiratory Failure, respectively, discuss the causes of hypoxemia further. The $PaCO_2$ may be decreased secondary to hyperventilation stimulated by hypoxemia and/or pulmonary receptors in the atelectatic regions.[3]

29.7.2 Radiography

Radiographic changes suggestive of atelectasis include mediastinal shift, elevation of the hemidiaphragm, rearrangement of the borders of the inflated lung lobes, increased lung density of the affected lobes, separation of the heart from the sternum, and asymmetry of the rib cage. Most signs of atelectasis are more easily seen in dorsoventral or ventrodorsal projections.[18] Some types of atelectasis do not result in radiographically detectable volume loss, because either the area of involvement is small or the collapsed alveoli have been infiltrated with fluid.

Positioning is important because a diseased lung positioned toward the table in an animal in lateral recumbency rapidly collapses.[18] In anesthetized animals an increase in lung density indicating partial collapse is common, and inflating the lungs a few times before radiographs are taken has been recommended.[19]

29.7.3 Computed Tomography

Computed tomography may be more sensitive than radiographs in detecting the presence and severity of atelectasis.

29.8 TREATMNET

So far as is possible, predisposing causes of atelectasis should be eliminated. Recumbent and critically ill patients have many factors predisposing to atelectasis such as recumbency, anesthesia, high inspired oxygen concentrations, and preexisting conditions. Anesthetized patients may also be at increased risk for atelectasis.

29.8.1 Oxygen

Although high concentrations of inspired oxygen may hasten alveolar collapse, oxygen therapy is an essential part of the management of hypoxemia caused by atelectasis. If airway obstruction is partial (low V/Q), hypoxemia is responsive to oxygen therapy.

29.8.2 Positive-Pressure Ventilation

If airway obstruction is complete (no V/Q, shunt) the condition is not responsive to oxygen therapy because the airways are occluded. If hypoxemia is severe positive-pressure ventilation is needed to open the closed airways and prevent recurrent collapse. Positive-pressure ventilation has been successful in atelectasis management, and positive end-expiratory pressure can be essential in reducing atelectasis in at-risk anesthetized patients.[20]

29.8.3 Airway Obstruction

Airway foreign bodies are often removed successfully with a variety of techniques, including direct visualization and retrieval, Heimlich maneuver, and bronchoscopy, providing the bronchoscope can be passed to the level of the obstruction. Bronchoscopy is used with varying success in human patients to remove airway secretions in an attempt to resolve atelectasis.[21] The applicability of this technique in veterinary patients is unknown at this time, but patient size may be a significant limitation.

29.8.4 Adjunctive Respiratory Therapy

The goals of multimodal approach to respiratory care are to improve gas exchange, minimize atelectasis, and promote clearance of secretions.[21] Adjunctive therapy includes the following:

- Frequent repositioning for recumbent patients
- Nebulization, chest percussion, and postural drainage
- Appropriate endotracheal suctioning
- Vital capacity maneuvers
- Positive end-expiratory pressure

29.8.5 Drugs

Bronchodilators, mucoactive agents, and antibiotics may be indicated, depending on individual patient needs.

29.9 SUGGESTED FURTHER READING*

J Aldrich, K Hopper, L Johnson, S Haskins: Successful ventilatory management of post-anesthetic airway collapse and hypoxemia in a dog. *J Vet Emerg Crit Care*. **12**, 2002, 105, *A description of the use of mechanical ventilation in the treatment of severe atelectasis.*

SG Hackner: Pulmonary thromboembolism. In LG King (Ed.): *Textbook of respiratory disease in dogs and cats*. 2004, Saunders, St Louis, *The first textbook dedicated to respiratory disease in dogs and cats. This chapter contains good detail and a review of the physiology and treatment of this condition.*

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AB Lumb: Parenchymal lung disease. In AB Lumb (Ed.): *Nunn's applied respiratory physiology*. ed 5, 2000, Butterworth Heinemann, Oxford, *New edition in keeping with the tradition of excellence of this authoritative text. Details of physiology in sufficient depth to satisfy most readers.*

WC Wilson, JL Benumof: Respiratory physiology and respiratory function during anesthesia. In RD Miller (Ed.): *Miller's anesthesia*. ed 6, 2005, Churchill Livingstone, New York, *A good source of information about the important, clinically relevant physiology*.

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* See the CD-ROM for a complete list of references.

30 Chapter 30 Pleural Space Disease

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30.1 KEY POINTS

- The pleural space is a potential space that contains a small amount of fluid and maintains a negative pressure.
- Clinical symptoms in animals with pleural space disease include tachypnea, open-mouth breathing, extended head and neck, crouched sternal recumbency with elbow abduction (orthopnea), cyanosis, and short, shallow breathing with an increased abdominal component. Thoracic auscultation often reveals muffled or absent breath sounds over affected areas of the thorax.
- Abnormalities within the pleural space may include pleural effusion, pneumothorax, or space-occupying soft tissue (diaphragmatic hernia, neoplasia). A diagnostic thoracentesis may also prove therapeutic in severely affected patients.
- Cytologic and fluid analysis should always be performed on aspirate from a newly diagnosed pleural effusion of unconfirmed etiology.
- Aerobic and anaerobic cultures with sensitivity testing of suppurative effusion are imperative.
- Pleural fluid triglyceride levels and cholesterol concentrations are necessary to establish the diagnosis of chylothorax.
- Clinical evidence of cardiovascular shock will often precede dyspnea in patients with hemothorax.
- Tension pneumothorax, regardless of its origin, may be rapidly fatal. Immediate thoracentesis is required before taking thoracic radiographs.
- Clinical signs of a traumatic diaphragmatic hernia may be delayed; however, early detection and correction are important because perioperative outcome is worse in patients with a preexisting hernia.

30.2 PLEURAL SPACE

The pleural space is a potential space formed by the parietal and visceral pleura. It normally contains a minimal amount (few milliliters) of serous fluid to facilitate motion of the lungs in relation to the thoracic cavity and to each other.[1] The pleura is a thin epithelium formed of mesothelial cells overlying a thin basal membrane. The pleura contain a superficial network of lymphatic ducts, blood vessels, and rare nerves.[2] The partition between the right and left hemithoraces is incomplete in small animals, but unilateral or unevenly distributed disease is common.[3]

30.2.1 Box 30-1 Modified Starling's Law Applied to the Pleural Cavity

Net filtration = $K\{[(P_{c\ parietal}-P_{c\ visceral})-P_{if}]-(\pi_c-\pi_{if})\}$

P_{cap}: capillary hydrostatic pressure of the visceral and parietal pleura

P_{if}: intrapleural hydrostatic pressure

π_{cap}: plasma oncotic pressure

π_{if}: intrapleural oncotic pressure

Modified from Pleural effusion and diseases of the pleura, *Vet Clin North Am Small Anim Pract* 15:1069, 1985.

Physiologic fluid flux in the pleural space is governed by Starling's law (Box 30-1). Hydrostatic pressure favors fluid accumulation within the pleural cavity (where pressure is subatmospheric), and the parietal pleura (systemic circulation) has greater filtration capacity than the visceral pleura (pulmonary circulation). However, oncotic pressure favors reabsorption of fluid from both pleura because the colloid osmotic pressure of the pleural space is 3.2 cm H_2O in dogs (compared with 24.5 to 27 cm H_2O in the vascular space). The visceral pleura assumes a larger role in determining the net pressure and favors reabsorption of fluid from the pleural space, where a greater vascular supply and lower hydrostatic pressure exist. Pleural lymphatic vessels are also an important component of fluid and blood reabsorption from the thorax.[3]

There is an average pleural pressure of –5 cm H_2O, representing the difference between the lung recoil and the thoracic cavity expanding forces, at rest.[4] Air, fluid, or soft tissue within the pleural space can cause the lungs to collapse and the chest wall to spring out by increasing the subatmospheric pressure within the thorax.[5] Pleural pathologies such as these subsequently lead to a decrease in tidal volume, total vital capacity, and functional residual capacity.[6] The resulting atelectasis can lead to both hypoxemia and hypoventilation.

30.3 CLINICAL EVALUATION

Clinical signs of pleural disease may include tachypnea, open-mouth breathing, extended head and neck, crouched sternal recumbency with elbow abduction (orthopnea), cyanosis, and short, shallow breathing with an increased abdominal component. The degree of dyspnea will vary depending on the amount of fluid, rate of fluid accumulation, and concurrent respiratory and metabolic disturbances. Auscultation reveals muffled breath sounds ventrally (fluid or tissue) or dorsally (air). Thoracic percussion reveals a low-pitched (fluid) or high-pitched (air) resonance of the affected area. The heart sounds may be muffled by fluid or tissue, or abnormally loud or displaced with unilateral or focal disease.

Thoracic radiographs are extremely helpful in diagnosing and quantifying pleural space disease and other intrathoracic pathology. Repeat radiographs after thoracentesis can be of diagnostic utility but were found to rarely be beneficial in providing additional diagnostic information in one human study.[7] Routine radiographs after thoracentesis are considered unnecessary for stable patients in the absence of suspicion, clinical indication, or risk factors for complications (mostly pneumothorax)[7,8] (Figure 30-1). Because the shape of the canine and feline chest is much different from that of humans, it is possible that dorsoventral radiographs in animals with pleural effusion (following thoracentesis) may still have improved diagnostic utility for evaluating the dorsal lung fields. Ultrasonographic examination is very helpful for rapid identification of pleural fluid in the emergency setting. In human medicine, indications for use of ultrasonographically guided thoracentesis include a small-volume effusion, inability to properly position the patient, failure of fluid to layer out on radiographs, and coagulopathy.[9] "In veterinary medicine, ultrasound guidance is used routinely to confirm the ideal point of needle insertion for thoracentesis, mostly in patients with a small volume of effusion, fluid pockets or those at increased risk for complications."

Thoracic ultrasonography may reveal underlying pathology such as a diaphragmatic hernia, neoplastic process, or lung lobe torsion.[10,11] Echocardiography will permit a diagnosis of cardiac disease, heart base tumor, and pericardial disease. Ultrasonography may also identify a pneumothorax by identifying the presence or absence of "lung sliding" (normal respiratory movement) at the lung surface.[12] Computed tomography is commonly used to characterize pleural and pulmonary lesions.[10] Thoracic scintigraphy is used mostly in small animal practice to identify pulmonary thromboembolism.[10] Thoracoscopy is another useful diagnostic and therapeutic tool in patients with pleural effusion and other intrathoracic pathology.[13]

Thoracentesis is an invaluable diagnostic, and often therapeutic, tool (see Chapter 31, Thoracentesis). Its indications include (1) the presence of any undiagnosed pleural effusion and (2) therapeutic thoracentesis to relieve respiratory signs caused by large amounts of air or fluid. However, if the etiology of the effusion is known and the patient is not dyspneic, the procedure may be delayed and the clinical signs followed.[14] Fluid analysis has great diagnostic utility in patients with pleural effusion of an undetermined etiology.[14,15]

30.4 PLEURAL EFFUSION

30.4.1 Pure Transudate and Modified Transudate

Transudative pleural effusion, or hydrothorax, is the result of variations in the Starling forces that govern pleural fluid flux (see Box 30-1). Pure transudates are characterized by a low total protein and total nucleated cell count (Table 30-1). Hydrothoraces generally develop secondary to decreased oncotic pressure within the vasculature and are commonly associated with hypoalbuminemia, although it also may be secondary to an increased hydrostatic pressure or neoplasia. Modified transudates are associated with an increased hydrostatic pressure (i.e., heart failure) or vascular permeability (e.g., vasculitis, lung lobe torsion, diaphragmatic hernia) causing leakage of a higher protein ultrafiltrate.[16] However, in animals with chronic effusion, irritation of the pleura may cause an increased nucleated cell count and water can be reabsorbed in excess of protein and cells.[6] Translocation of abdominal effusion, neoplastic effusion, and chylothorax are other causes of transudates.

30.4.2 Exudates

Exudative effusions are the result of chemotactant (causing white blood cell accumulation) and vasoactive substances (causing high-protein fluid efflux) within the pleural cavity secondary to an inflammatory process. Degenerate neutrophils usually will predominate with a bacterial infection.[16] Bacteria may originate from hematogenous or lymphatic spread, penetrating insults (iatrogenic, inhaled or external foreign body, bite wound, trauma), or spread from infected organs (lung, gastrointestinal).[16] Aerobic and anaerobic cultures are recommended for all exudates. *Nocardia* spp, *Actinomyces* spp, and *Fusobacterium* spp are filamentous rods that are difficult to grow on culture media or identify with culture, cytologic, or histologic examination.[16,17] Other types of organisms, such as fungi, protozoa, and rickettsiae, may also cause septic pleural exudates.[16]

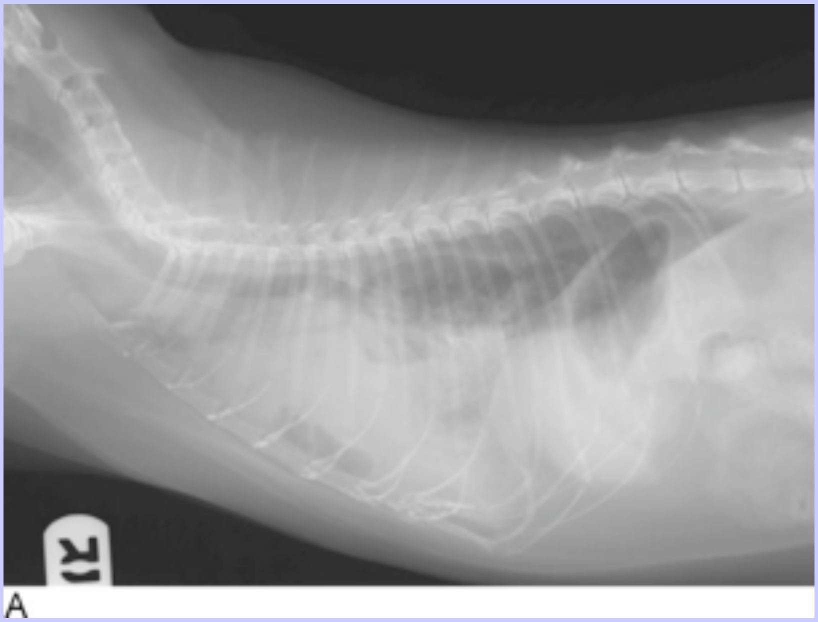
In aseptic exudates, the predominant cell type may vary to include nondegenerate neutrophils (inflammation), small lymphocytes (chylothorax), or neoplastic cells. Potential causes of an aseptic exudate include pneumonia and other well-circumscribed infections (e.g., abscess), generalized sepsis, pancreatitis, or necrosis of intracavitary neoplasia.[16]

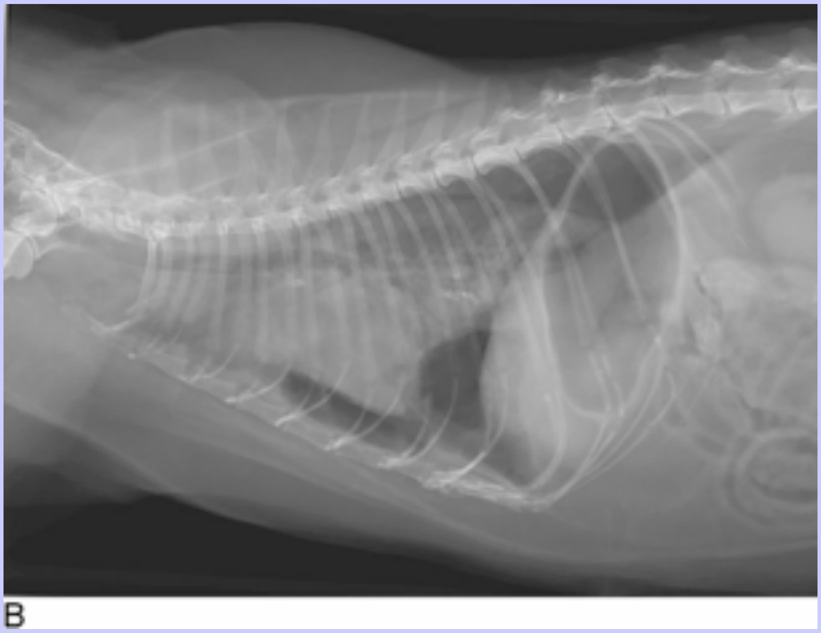
30.4.3 Feline Infectious Peritonitis

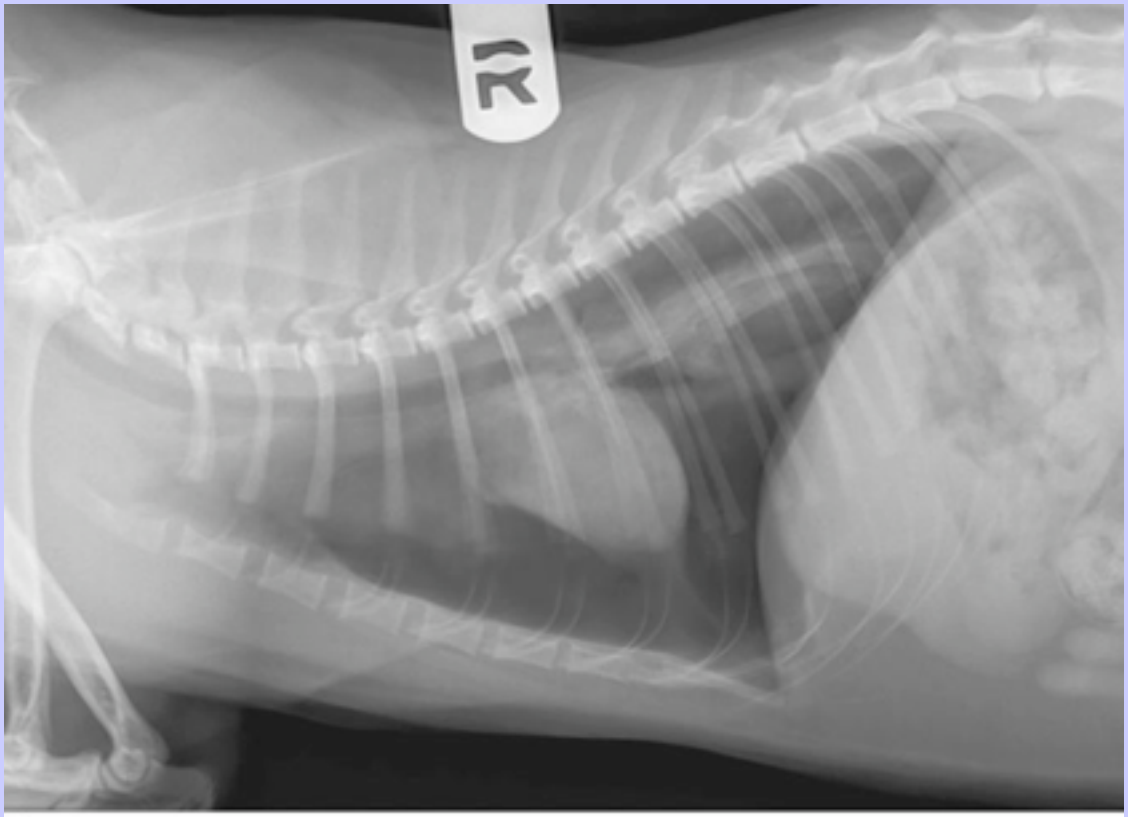
Feline infectious peritonitis (FIP), caused by a coronavirus (feline immunodeficiency virus [FIPV] or feline coronavirus [FCoV]), is a common cause of aseptic pleural exudative effusion in cats, but it may also cause a modified transudate. Abdominal and pericardial effusion can be concomitant. The effusive form is a more acute disease process but may be present terminally in noneffusive FIP.[17] The effusive form results from either a greater viral load causing a larger quantity of circulating immune complexes or an ineffective cell-mediated immune response.[17,18] Deposition of infected macrophages and immune complexes on the endothelium result in complement-mediated, severe pyogranulomatous vasculitis.[18]

FIP is most often found in young, purebred, intact males.[19] Clinical signs will vary depending on the form and organ systems affected. Pleural or peritoneal fluid typically will be viscous, straw-colored, and have a high protein concentration (>3.5 g/dl) with a relatively low nucleated cell count (<5000 cells/ml).[17] Nondegenerate neutrophils predominate in the fluid, with or without macrophages and lymphocytes.[17] Immunofluorescent staining of intracellular FCoV antigen has high specificity, and anti-FCoV antibody testing has both high positive and negative predictive values.[20] The highest serum antibody titer (1:1600) is an excellent predictor of disease, and reverse transcriptase polymerase chain reaction on the effusion has shown promising results although false results are possible.[20] Histopathology remains the gold standard for diagnosing this disease.[18] The prognosis for recovery is grave; however, a new treatment protocol including feline recombinant interferon-ω and glucocorticoids has been described in a small group of cats, with more promising results.[21]

Figure 30-1 Cats with pleural space disease. **A,** Moderate volume of malignant effusion secondary to bronchogenic adenocarcinoma. **B,** Pneumothorax after thoracentesis in the patient shown in *A*. **C,** Traumatic pneumothorax from high-rise syndrome. **D,** Spontaneous pneumothorax from diffuse pulmonary metastasis of salivary gland adenocarcinoma.







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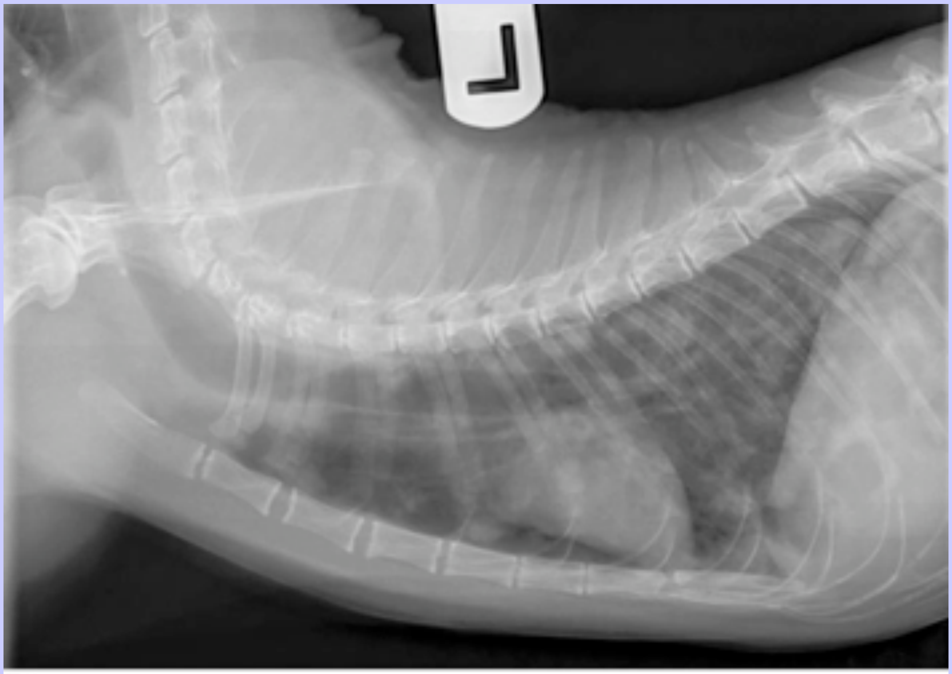

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Table 30-1 Fluid Type and Characteristics[16]

Fluid Type	Fluid Characteristics
Pure transudate	TP <2.5 g/dl TNCC <1500/µl
Modified transudate	TP 2.5 to 7.5 g/dl TNCC 1000 to 7000/µl
Exudate	TP >3.0 g/dl TNCC >7000/µl

TP, Total protein; *TNCC,* total nucleated cell count.

30.4.4 Pyothorax

A pyothorax is defined as an accumulation of purulent exudate within the thoracic cavity. Bacterial infection within a feline thorax is most often the result of bite wounds in young cats from multicat households.[22] Migrating inhaled foreign bodies, and traumatic thoracic penetration are more frequent in dogs.[23,24] Young adult hunting or working breeds are over-represented.[25] Other bacterial sources reported include pneumonia, pleuropneumonia, lung abscess, aberrant migration of *Cuterebra* larvae or grass awns, hematogenous or lymphatic dissemination, esophageal or tracheal perforations, lung parasites, diskospondylitis, neoplasia with abscess formation, and iatrogenic causes.[22-24] Septic suppurative effusion typically is diagnosed when intracellular organisms are present on cytologic examination and the presence of intracellular organisms. Culture and sensitivity testing should be performed on the fluid and antibiotic therapy initiated. Ancillary tests such as glucose and lactate levels and pH may also be helpful to diagnose the presence of sepsis.[25,28] Anaerobic bacteria 127
are found most commonly,[25,26] and infections with multiple organisms are highly prevalent.[22,25] In cats, 128
nonenteric bacteria are most common and *Pasteurella* spp is most frequently isolated.[22,26] In dogs, *Escherichia coli* and other members of the family Enterobacteriaceae are isolated most often.[26,27]

Hospitalization for appropriate supportive care and intravenous antibiotics is indicated. Pending culture and sensitivity results, broad spectrum intravenous antibiotic therapy, such as enrofloxacin for gram-negative bacteria and ampicillin with sulbactam or ticarcillin with clavulanate for gram-positive and anaerobic infections,[29] should be instituted as soon as possible. However, an increasing resistance of *E. coli* to enrofloxacin has been documented, and amikacin and ceftizoxime have shown to have better efficacy against this organism.[26] Clindamycin is also effective against many of the offending organisms in cats. Medical management with thoracostomy tubes (bilateral in most cases) is recommended, and sterile lavage with physiologic saline (10 to 20 ml/kg q6-12h daily) may be used initially if the effusion is thick and flocculent (see Chapter 32, Thoracostomy Tube Placement and Drainage). Absorbed lavage solution by the inflamed pleura can lead to fluid overload, so close monitoring of fluid “ins and outs” is recommended. Intermittent thoracentesis is not a recommended means of drainage and is associated with increased mortality.[17] Tubes will often be necessary for 4 to 6 days,[22,25,27] and removal is based on daily fluid reevaluation and the quantity of fluid produced (<2.2 ml/kg per tube q24h, although this can vary depending on the severity of pleuritis).[30] Thoracic radiographs or ultrasonographic examination should be used to monitor the efficacy of drainage. A thoracotomy should be performed if pocketed fluid is persistently not drained by the thoracostomy tubes; if lung or pleural abscess, foreign body, or neoplasia is suspected; or if medical management is failing.

In cats with a pyothorax, reported survival is 66.1% overall, 77.6% after the first 24 hours of hospitalization. A lower heart rate and hypersalivation were associated with death, and a higher white blood cell count was associated with survival. The need for surgical exploration has not been associated with poorer outcome, and recurrence is rare (5.9%).[22] In dogs, surgical treatment is associated with a better outcome: 78% were disease free after 1 year versus 25% with medical treatment.[27]

30.4.5 Chylothorax

Chylous effusion is opaque and white or pink. Small lymphocytes usually predominate; however, nondegenerate neutrophils may become predominant after repeated thoracocenteses or with chronic disease.[16] The triglyceride concentration within the effusion is higher than the concentration in the serum, while the cholesterol level is equal to or lower than that of the serum. Causes of chylothorax include heart disease (cardiomyopathy, congestive heart failure, pericardial disease), thoracic duct obstruction (intraluminal neoplasia or granuloma or extraluminal), traumatic rupture of the thoracic duct, cranial mediastinal mass (thymoma, lymphosarcoma, aortic body tumor), lung lobe torsion, diaphragmatic or peritoneopericardial hernia, post–pacemaker implantation in cats, heartworm disease, congenital malformations, cranial vena caval thromboembolism, ligation of the left brachiocephalic vein, and idiopathic contributors.[31,32]

Idiopathic chylous effusion is diagnosed by exclusion in most animals with true chylothorax.[33] Medical management consists of intermittent thoracentesis, a reduced-fat diet, and rutin (a benzopyrone). Rutin is a nutraceutical that stimulates macrophage breakdown of protein in lymph, accelerating its reabsorption.[31,34] Thoracostomy tubes are indicated only in animals with a traumatic chylothorax, if thoracentesis is required several times weekly, or following surgery.[6] Surgical intervention is recommended if the medical management is unsuccessful at providing good quality of life to the animal. Multiple interventions have been described, however a recent study has shown improved success rates with a combination of thoracic duct ligation and subtotal pericardectomy (100% of dogs and 80% of cats had resolution of pleural fluid accumulation for at least 60 days following the procedure).[33] Other surgical interventions reported include omentalization, passive pleuroperitoneal shunt, active pleuroperitoneal or pleurovenous shunt, and pleurodesis, but these procedures have shown a worse outcome.[31,33] Thoracoscopic ligation of the thoracic duct has been described in an experimental study.[35]

Complications of chylous effusion and its drainage include weight loss, electrolyte abnormalities (pseudoaddisonian), lymphopenia, hypoproteinemia, dehydration, and fibrosing pleuritis.[31] Rarely, spontaneous resolution of idiopathic effusion occurs. This is expected in most animals suffering from traumatic thoracic duct rupture.

30.4.6 Hemothorax

A hemothorax is defined as a pleural space effusion with a hematocrit that is 25% greater than that of the peripheral blood.[6] Evidence of erythrophagocytosis and absence of clotting or platelets on cytologic examination differentiate iatrogenic hemorrhage from a true hemorrhagic effusion (unless peracute). Hemorrhage within the pleural cavity can be caused by a severe coagulopathy, often associated with ingestion of an anticoagulant rodenticide that causes vitamin K epoxide reductase inhibition. Blunt or penetrating trauma, diaphragmatic hernia, thymic hemorrhage, neoplasia, pulmonary thromboembolism, lung lobe torsion, and dirofilariasis are other reported causes. Finally, iatrogenic hemorrhage may be caused by venipuncture, jugular catheter placement, Swan-Ganz catheter placement, thoracentesis, intrathoracic biopsy, intrathoracic fine-needle aspiration, and following thoracostomy or herniorrhaphy.

Cardiovascular shock often precedes respiratory compromise because as much as 30 to 60 ml/kg (dogs) or 20 ml/kg (cats) of pleural effusion is required to impair ventilation in those with normal pulmonary parenchyma.[36,37] Therefore treatment includes appropriate fluid resuscitation and blood transfusions as needed. Only sufficient blood should be retrieved from the pleural space to relieve dyspnea and allow adequate oxygenation, because the red blood cells that remain will be reabsorbed over the ensuing several days. Autotransfusion should be considered in trauma patients if more than 10 ml/kg of effusion is present.[36] Thoracostomy tube placement should be considered if the animal cannot be stabilized with thoracentesis and the hemorrhage is ongoing (see Chapter 32, Thoracostomy Tube Placement and Drainage). Surgery is rarely indicated with traumatic hemothorax unless a penetrating injury or uncontrollable hemorrhage is present.

30.4.7 Neoplastic Effusions and Pleural Neoplasia

Intrathoracic neoplasia may result in transudates or exudates by causing increased vascular permeability, obstruction of pleural and pulmonary lymphatic vessels or veins, shedding of necrotic material at the pleural surface (increasing oncotic pressure within pleural space), and obstruction or perforation of the thoracic duct.[38] Hemorrhage and pneumothorax may also result from neoplasia. Common primary thoracic cancers include mesothelioma, pulmonary carcinomas, and lymphosarcoma, but metastatic disease can also result in pleural abnormalities. Fluid analysis and cytologic studies are informative, but thoracic ultrasonography and computed tomography with fine-needle aspiration or biopsy will often be necessary to obtain a definitive diagnosis.

30.4.8 Fibrosing Pleuritis

Fibrosing pleuritis is a chronic condition in which the visceral pleura becomes thickened and restricts lung expansion as a result of inflammation within the thoracic cavity. Causes of this condition in humans include chylothorax, hemothorax, pleural infection, drugs, neoplasia, asbestosis, rheumatoid pleurisy, coronary bypass surgery, and uremia.[38] In veterinary medicine, this pathology is most frequently associated with chylous effusion.[39] Development of fibrosis depends on the degree of mesothelial cell and basement membrane damage and regeneration. A disorder of fibrin turnover is thought to lead to deposition of the intrapleural fibrin matrix.[39] Radiographs will show rounded, retracted lung lobe(s) that will not expand following thoracentesis. Pulmonary edema and interstitial fibrosis may contribute to dyspnea.[40] Decortication is the only successful therapy in humans and should be considered early for better outcome, while pulmonary changes are minimal. Pneumothorax is a common complication and reexpansion pulmonary edema is also possible. The prognosis is guarded with diffuse disease.[40]

30.5 PNEUMOTHORAX

A pneumothorax is open if it results from an insult to the thoracic wall, such as a penetrating thoracic trauma. In patients with a closed pneumothorax, the thoracic cavity is intact and the air originates from a lesion within the lung parenchyma, trachea, airways, esophagus, mediastinum, or diaphragm. A tension pneumothorax develops if the site of air leakage creates a one-way valve during inspiration and results in a rapidly increasing pleural pressure that exceeds atmospheric pressure.

Traumatic pneumothorax is a common sequela of motor vehicular accidents and was found concurrently in 47% of dogs with pulmonary contusions.[41] It has also been reported in most (63%) cats with high-rise syndrome.[42] External wounds, such as a projectile injury, bite wounds, and penetrating sharp objects to the thorax and cervical spine, are also frequent causes. Iatrogenic pneumothorax following thoracentesis is common, with an incidence of 3% to 20% in humans, with approximately 20% of those patients requiring a thoracostomy tube(s) placement.[14] Other common iatrogenic causes include leakage following lung lobectomy or respiratory tract surgery, thoracostomy tubes, fine-needle lung aspiration, barotrauma during positive-pressure ventilation, and tracheal tears. Spontaneous pneumothorax is most often associated with pulmonary bullous emphysema in dogs, with the Siberian Husky being overrepresented.[43] Multiple other pathologic conditions can lead to a spontaneous pneumothorax: neoplasia, feline asthma, pulmonary abscess, heartworm disease and other parasitic infections, foreign body migration, subpleural blebs, and pneumonia.[6] Finally, an infectious pneumothorax can be created by gas-forming bacteria within the thoracic cavity.

A tension pneumothorax can rapidly become life threatening, and immediate thoracentesis is indicated in animals suspected to have this condition. If the pneumothorax is not easily relieved with thoracentesis, an emergency minithoracostomy, with intubation and mechanical ventilation may prove lifesaving. Decreased venous return to the thorax in animals with a tension pneumothorax can be associated with cardiovascular collapse and shock. The thorax may become barrel shaped, and limited chest expansion is noted despite significant respiratory effort. However, animals with subclinical air accumulation may not require thoracentesis and the animal's progression should be followed closely because the air will be reabsorbed over days to weeks. A small amount of air in animals with severe pulmonary pathology may contribute significantly to dyspnea and should be relieved. Most patients with a closed traumatic or iatrogenic pneumothorax require thoracentesis only once or twice.

Animals should be monitored closely after thoracentesis for return of dyspnea, and cage rest is recommended for 2 weeks. The indications for a thoracostomy tube vary according to the clinical situation, but a tube should be placed in patients requiring more than two thoracocenteses within 6 to 12 hours (see Chapter 32, Thoracostomy Tube Placement and Drainage). Other indications include patients with a tension pneumothorax and those with a pneumothorax that require mechanical ventilation.

Constant negative pressure applied within the pleural cavity is recommended using a two-chambered or three-chambered continuous suction device, or commercially available Pleur-evac. Alternatively, a Heimlich valve may be used in medium and large breed dogs (although caution should be exercised if fluid accumulation is also present within the pleural space).

An exploratory thoracostomy is indicated if a closed traumatic pneumothorax does not resolve after 3 to 5 days of drainage. If an open pneumothorax is caused by a penetrating injury, the injury should be covered with an occlusive bandage, thoracentesis performed, and surgical repair is required as soon as the patient is stable. A spontaneous pneumothorax in dogs is best treated with surgical exploration, leading to a higher survival rate and decreased recurrence.[43] Thoracoscopic lobectomy has also been described in these patients.[44] Overall prognosis is good, with an 86% survival rate for treated dogs and cats with various causes of air accumulation. Favorable prognostic factors included absence of dyspnea, no need for thoracentesis, longer intensive care stay for dogs, and normal body temperature on admission in cats.[45]

30.6 SPACE-OCCUPYING LESIONS

Space-occupying lesions within the pleural space may occur secondary to benign or malignant masses within the mediastinum or chest wall. These typically are diagnosed with thoracic radiographs or computed tomography. Further details on these diseases are beyond the scope of this chapter.

30.7 DIAPHRAGMATIC HERNIA

Acquired diaphragmatic hernias are usually the result of blunt trauma associated with vehicular trauma, high-rise syndrome, or dog fighting or attacks, but may also be iatrogenic. Congenital diaphragmatic hernias are a result of aberrant embryogenesis and may be pleuroperitoneal, peritoneopericardial, or hiatal. These hernias are rare and beyond the scope of this chapter.

Clinical signs may occur immediately after the traumatic event, but are considered chronic if present for more than 2 weeks.[46,47] Dyspnea varies from none to severe according to the organ herniated, resulting pleural effusion, and concomitant thoracic injuries. The organs most frequently involved are the liver, stomach, and small intestine; the omentum and spleen are also frequently herniated.[46-48] On physical examination, borborygmus over the chest or asymmetrically quiet heart and/or lung sounds may be auscultated. The abdomen may be further tucked in or palpated “empty,” with failure to distinguish certain organs. Thoracic radiographs may reveal gas-filled abdominal organs within the thorax, an incomplete diaphragmatic border, pleural effusion, and/or cranially displaced abdominal organs. Additional radiographic views, ultrasonography, positive contrast celiography, and an upper gastrointestinal contrast study may aid in the diagnosis.

Thoracentesis and gastrocentesis may relieve the dyspnea prior to surgery. Cardiovascular stabilization prior to surgery is also important. Indications for immediate surgical intervention include herniated stomach, strangulated bowel or organs, inability to oxygenate properly after medical intervention, and ruptured viscera. Most data suggest that early surgical intervention (within 24 hours of admission) provides an excellent prognosis for acute cases.[47]

Postoperative complications include pneumothorax, hemorrhage, aspiration pneumonia, sepsis, arrhythmias, and death.[46-48] Reexpansion pulmonary edema (RPE) is a rare complication following surgery. It results from release of endotoxins and oxygen free radicals released, decreased surfactant concentrations, negative interstitial pressures, and/or chronic hypoxia causing increased vascular permeability and protein-rich pulmonary edema. Increased incidence of RPE has been associated with a longer duration of collapsed lung (≥72 hours). Care should be given to keep peak airway pressure below 20 cm H_2O to avoid positive end-expiratory pressure, and pleural air should be slowly evacuated postoperatively (>12 hours).[49] Prognosis for full recovery is excellent for acute cases (survival rate 94%).[47] Perioperative survival rate is lower (82% to 89%) when chronic acquired cases are included in the statistical analysis.[46-48] In some studies, dyspnea did not affect prognosis,[47] but older age, lower respiratory rate, and concurrent multiple injuries were associated with higher mortality in cats.[48]

30.8 SUGGESTED FURTHER READING*

American Thoracic Society: Guidelines for thoracocentesis and needle biopsy of the pleura. *Am Rev Respir Dis*. **140**, 1989, 257, *Position of the Board of Directors of the American Thoracic Society (June 1988).*

TW Fossum, MM Mertens, MW Miller: Thoracic duct ligation and pericardectomy for treatment of idiopathic chylothorax. *J Vet Intern Med*. **18**, 2004, 307, *Prospective study of 20 animals (10 dogs and 10 cats) with idiopathic chylous effusion*.

TWG Gibson, BA Brisson, W Sears: Perioperative survival rates after surgery for diaphragmatic hernia in dogs and cats: 92 cases (1990-2002). *J Am Vet Med Assoc*. **227**, 2005, 105, *Retrospective study evaluating survival rate in patients with traumatic diaphragmatic hernia when surgical correction occurred within 24 hours of admission*.

DA Puerto, DJ Brockman, C Lindquist, et al.: Surgical and nonsurgical management of and selected risk factors for spontaneous pneumothorax in dogs: 64 cases (1986-1999). *J Am Vet Med Assoc*. **220**, 2002, 1670, *Retrospective study*.

LS Waddell, CA Brady, KJ Drobatz: Risk factors, prognostic indicators, and outcome of pyothorax in cats: 80 cases (1986-1999). *J Am Vet Med Assoc*. **221**, 2002, 819, *Retrospective study*.

* See the CD-ROM for a complete list of references.

31 Chapter 31 Thoracentesis

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31.1 KEY POINTS

- Thoracentesis is an easily performed diagnostic and therapeutic procedure and is safe if performed by skilled personnel.
- Blind thoracentesis is performed between the seventh and ninth intercostal spaces.
- Thoracentesis for fluid removal is best guided by ultrasonography.
- Strict aseptic technique is required.
- Indications for thoracentesis are pneumothorax and pleural effusions (chyle, transudate, blood).
- Contraindications to thoracentesis include severe coagulopathies, thrombocytopenia, and thrombocytopathia.

31.2 INTRODUCTION

The removal of fluid or air by puncturing the chest with a hollow needle, catheter, or tube is called *thoracentesis,* and it can be used as both a diagnostic tool and a therapeutic intervention.[1] In contrast to the emergency patient, pleural effusions are more common than pneumothorax in the critically ill patient.[1,2] In this patient population, pleural effusion may be caused by the primary disease process or can have secondary cardiovascular or iatrogenic causes. In humans, pleural effusions commonly accompany edematous states due to heart failure or volume overload, pneumonia, or acute respiratory distress syndrome.[2] Thoracentesis is an easy and potentially lifesaving procedure that every emergency and critical care veterinarian should be able to perform. Several techniques are discussed in this chapter.[3,4]

31.3 INDICATIONS

Animals with pleural space disease experience respiratory distress and may show an inward abdominal movement during inspiration. Other animals (especially cats) often show superficial and fast breathing. On auscultation, decreased lung sounds may be heard unilaterally or bilaterally. Lung sounds are generally decreased in the dorsal lung fields in association with pneumothorax and in the ventral regions of the chest in association with pleural effusion. Other clinical signs such as a heart murmur, distended jugular veins, increased lung sounds, coughing, bowel sounds heard during chest auscultation, or the feeling of missing organs on abdominal palpation might help in the differentiation of pleural space diseases. Thoracic radiographs, ultrasonography, echocardiography, packed cell volume and total solids, and albumin measurements may further help identify the cause of respiratory distress and the need for thoracentesis. Thoracentesis can be an important diagnostic and life- saving therapeutic intervention in the animal with severe respiratory distress and should not be withheld in the absence of a confirmed diagnosis of pleural space disease.

31.3.1

Box 31-1 Equipment Needed for Thoracentesis

- Clippers
- Surgical prep solution
- Lidocaine (1% to 2%)
- Gloves (sterile)
- Butterfly needle or over-the-needle catheter or hypodermic needle of appropriate size
- Extension set
- Three-way stopcock
- 10- to 60-cc syringe, depending on patient size and expected amount of fluid or air
- Tubes for fluid analysis (ethylenediaminetetraacetic acid, heparin, sterile tube for bacterial culture)
- Sterile saline (if using the needle technique)

Indications for thoracentesis are diagnosis or suspicion of pneumothorax, tension pneumothorax, or pleural effusion.[1,3] Pneumothorax can be traumatic or spontaneous in nature. Pleural effusion can arise from heart failure, inflammation associated with pneumonia, pancreatitis, pyothorax or feline infectious peritonitis, chylothorax, neoplasia, bleeding disorders, trauma, or lung lobe torsion.[2,5] Thoracentesis is indicated when air or fluid accumulation in the pleural space is believed to be causing or contributing to respiratory difficulties. Diagnostic thoracentesis in critically ill patients is indicated for pleural effusions that cannot be otherwise explained. Treatment of suspected infectious processes such as feline infectious peritonitis and pyothorax will usually include pleural drainage.[2,3]

Relative contraindications are pleural space diseases that cannot be treated by thoracentesis. These include pneumomediastinum, diaphragmatic hernia without fluid accumulation, and pleural masses. Other possible contraindications are bleeding disorders and large bullae because they may lead to deterioration of the patient's respiratory status.[1]

31.4 MATERIALS

If not already initiated, supplemental oxygen should be administered to all patients before any handling or restraint.[3] Material for orotracheal intubation, including a functional strong light source, should be prepared and ready to use when handling dyspneic patients. The required materials for the procedure should be prepared before handling the patient. Equipment needed for thoracentesis is summarized in Box 31-1.

Thoracentesis is performed with a needle, peripheral catheter, or flexible tube placed within the pleural space.[1] It is generally recommended to use the smallest gauge catheter or needle possible.[1] For example, to aspirate air, a 22-gauge butterfly needle can be used in cats and small dogs, and an 18-gauge butterfly needle may be effective in medium and large dogs. The catheter size is generally increased for the aspiration of pleural effusions.

Thoracentesis requires a minimum of two, and ideally three, people. One person is needed to restrain and limit patient movement, one to place and stabilize the needle, and one to aspirate and collect the fluid or air. The person operating the syringe and stopcock needs both hands, so if only two people are available, the person doing the tap and holding the needle in place also has to restrain the patient.

31.5 TECHNIQUES

The time of intervention has to be coordinated with all members of the team in order to minimize patient stress. The animal should choose its most comfortable position. Thoracentesis can be done with an animal standing, sitting, or lying on its side.[3] The region of the tap is clipped and aseptically prepared. The only exemption to this is an animal in severe respiratory distress in which the clinical signs do not allow time for surgical preparation. The anatomic site for thoracentesis should be based on auscultation results, position of the animal, and the nature of the suspected problem. Blind thoracentesis is performed at intercostal spaces 7 to 9 (Color Plate 31-1, *A*). If a pneumothorax is suspected, then the needle is inserted in the mid to upper thorax.[3] Fluid may be best aspirated in the lower third of the chest and fluid thoracentesis should be performed under ultrasonographic guidance whenever possible. When ventral thoracentesis is performed, care must be taken to avoid the internal thoracic arteries, which run along the ventral thorax, a few centimeters either side of the sternum, because laceration of this artery can result in significant hemorrhage.[3]

Before puncture, the subcutaneous tissue and the pleura can be infiltrated with a local anesthetic such as lidocaine (1 to 2 mg/kg).[1,3] The puncture site should be cranial to the rib or in the middle of the intercostal space in order to minimize damage to vessels and nerves located caudally to every rib.[1,6]

Several techniques for thoracentesis are described.[1,3,4,7,8]

31.5.1 Needle Insertion Techniques

31.5.1.1 Thoracentesis Using a Butterfly Needle

Using a butterfly needle, the three-way stopcock and syringe can be attached before the puncture is performed (see Color Plate 31-1, *A*). The needle is inserted through the skin and slowly advanced into the pleural space while gentle negative pressure is applied with the syringe (Color Plate 31-1, *B*).[4, 7] The needle is advanced until either it feels like the pleura has been penetrated or air or fluid can be aspirated. Once the pleural space has been entered, the needle is angled so that it is lying flat against the chest wall (directed caudally or ventrally) with the needle bevel directed away from the chest wall (Color Plate 31-1, *C*). Aspiration is performed gently and is stopped if negative pressure is obtained or the lung can be felt scratching against the needle.

The author prefers this technique for thoracentesis because it is fast and relatively safe. The short needle is an advantage in small animals but might be too short in large dogs. In large dogs, a hypodermic needle connected to an extension set and collection system can be used as an alternative.[3]

31.5.1.2 Thoracentesis Using a Hypodermic Needle with a Saline-Filled Hub

The hub of a hypodermic needle is filled with sterile saline before slowly advancing the needle through the skin. The needle is advanced until the saline is either sucked inward (indicating entry into the pleural space) or expelled (indicating a tension pneumothorax). The needle is then directed in a caudal direction. The extension tubing and stopcock are connected to the needle, and aspiration is performed as described above.[3]

31.5.2 Over-the-Needle Catheter Insertion Technique

31.5.2.1 Thoracentesis Using an Over-the-Needle Intravenous Catheter

Over-the-needle catheters are available in a variety of sizes and lengths and following placement provide a relatively atraumatic option for thoracentesis. An 18-gauge catheter is recommended for cats and small dogs, a 16-gauge catheter for medium size dogs and a 14-gauge catheter for large dogs. An over-the-needle catheter is advanced through a small relief incision and into the pleural space. Location in the pleural space is confirmed by removal of the stylet and aspiration of fluid or air after connection of the extension tubing and stopcock to the catheter. Alternatively the extension set can be connected to the stylet and gentle suction applied while advancing the catheter into the pleural space. When air or fluid is aspirated, indicating entry into the pleural space, the stylet is retracted a short distance such that the point of the stylet is enclosed within the catheter. The catheter and stylet are then advanced together in a ventral direction as a unit. Once fully inserted, the stylet is removed and the extension set is connected to the catheter.[1] Over-the-needle catheters can be fenestrated with a scalpel blade to improve the ability to aspirate viscous pleural effusions. Care must be taken to make the fenestrations small, evenly spaced and smooth.

31.5.2.2 Thoracentesis Using a Thoracentesis Tube

Commercially available thoracentesis tubes with several holes at the tip can be used for drainage of large amounts of fluid or air. These tubes have a sharp stylet or trochar that can be used for insertion of the tube into the pleural cavity. Once the tube enters the pleural space, the stylet is held in place and the tube is advanced over the stylet.[2]

31.5.3 Through-the-Needle Catheter Technique

This technique uses a 14- to 18-gauge introducer needle through which a flexible catheter is inserted once the needle enters the pleural space. First the catheter is connected to the extension set, three-way stopcock, and syringe, and then it is set aside. A second syringe is then attached to the empty introducer needle, and gentle suction is applied while the needle is entered into the pleural space. Once fluid or air can be aspirated, the needle 132
is held in place, the aspiration syringe is detached, and the catheter is inserted quickly through the needle into the 133
pleural space and advanced as far as possible. The needle is then withdrawn from the chest, leaving the catheter in place.[1]

31.5.4 Seldinger Technique

The Seldinger technique may be indicated to drain large amounts of fluid or air.[9] A guidewire is fed through a needle (similar to the technique above) into the pleural space. The needle is then removed, leaving the guidewire in place. A flexible catheter with several holes at the tip is then inserted over the guidewire. Once the catheter is inserted into the pleural space the guidewire is removed and the drainage tubing can be connected. This technique is rarely used for thoracentesis but might be an option in animals that require aspiration of large amounts of fluid when a thoracotomy tube is not possible or not desired.

Whatever procedure is used, once the needle has entered the pleural space, the entire needle should be placed parallel to the body wall with the bevel directed toward the lung to avoid iatrogenic lung laceration or puncture (see Color Plate 31-1, *C*).[7] It might be necessary to redirect the needle, however, and this must be done with the length of the needle parallel to the thoracic wall. Once negative pressure is achieved or the lung can be felt scratching at the needle, it is important to stop aspiration and to remove the needle in the flat position in order to decrease the risk of lung laceration.[7] Usually, the thorax is emptied maximally, which might require bilateral thoracentesis.

The amount of aspirated air or fluid should be measured and diagnostic evaluation of fluid initiated. Specific gravity, packed cell volume, cell count, total solid measurement, cytologic evaluation, and aerobic and anaerobic culture testing may be indicated.

In case of a negative result on thoracentesis and strong suspicion for pneumothorax or pleural effusion, it is recommended to repeat the procedure at another location.

31.6 POSTPROCEDURE CARE

Routine thoracic radiographs may not be essential, however they can be helpful in determining the cause of pleural space disease after fluid or air has been removed. They are also indicated in cases of unsuccessful thoracentesis. Postprocedure chest radiographs are recommended in human patients who are being ventilated, and this may be a consideration for veterinary patients as well.[2]

After thoracentesis, the thorax is auscultated on a regular basis and respiratory rate and effort are monitored. Thoracentesis should be repeated whenever the patient's respiratory status deteriorates. If repeated thoracentesis is necessary, chest tube placement should be considered.

31.7 COMPLICATIONS

Thoracentesis in human patients can have a high complication rate.[2] Pneumothorax and arterial laceration causing hemothorax are the most common complications.[1] The rate of pneumothorax after thoracentesis has been reported to be as high as 30% in human patients.[2] This rate can be diminished to 0% to 3% using ultrasonographic guidance when thoracentesis is done for pleural effusion.[2] Pneumothorax can occur as a result of laceration of the lung by the needle, by introduction of air through the needle or catheter system, by puncture of a bulla, or by exertion of extreme negative pressure with an nonexpandable lung, leading to pressure-related lung laceration.[1]

Hypotension and reexpansion pulmonary edema may occur if a large volume of fluid or air is evacuated in cases of chronic pleural space disease.[1,2] Vagal reactions have also been reported. Minor complications include formation of a hematoma or seroma at the puncture site. The incidence of complications of thoracentesis in animals has not been reported.

In the author's opinion, more animals are lost by not doing a thoracentesis than by performing an unnecessary thoracentesis, provided appropriate technique and asepsis are used. Thoracentesis performed by experienced personnel is a safe, simple, and potentially lifesaving technique.

31.8 SUGGESTED FURTHER READING*

B Blok, A Ibrado: Thoracentesis. In JR Roberts, JR Hedges (Eds.): *Clinical procedures in emergency medicine*. 2004, Saunders, Philadelphia, *The human emergency procedures “bible” that describes several techniques and discusses indications. Nice illustrations; however, the techniques used in human medicine have to be adapted to veterinary patients*.

DT Crowe, JJ Devey: Thoracic drainage. In MJ Bojrab (Ed.): *Current techniques in small animal surgery*. 1998, Williams & Wilkins, Baltimore, *A textbook chapter that discusses indications, technique, and complications of thoracentesis in small animals*.

C Orton: Pleural drainage. In C Orton (Ed.): *Small animal thoracic surgery*. 1995, Williams & Wilkins, Baltimore, *A textbook chapter that reviews techniques for thoracentesis and chest tube placement and setting up a drainage system*.

* See the CD-ROM for a complete list of references.

32 Chapter 32 Thoracostomy Tube Placement and Drainage

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32.1 KEY POINTS

- Chest tubes are used to remove air or fluid from the pleural space.
- The diameter of a chest tube should be similar to the size of the mainstem bronchus. Smaller diameter tubes can be used for a simple pneumothorax; larger diameters are used to drain viscous fluid such as purulent exudate.
- Chest tubes are best inserted in an anesthetized and intubated animal. Sedation and local anesthesia may be sufficient in some cases.
- Several tubes and placement techniques exist.
- Thoracic radiographs are recommended following tube placement.
- Suction can occur on a continuous or intermittent basis.
- Patients with chest tubes need 24-hour monitoring.
- Strict aseptic placement and management are required.

32.2 INTRODUCTION

Therapeutic drainage of the pleural space dates back more than 200 years, and the technique of chest tube placement for various indications has been adapted and perfected since then.[1] Thoracostomy tubes, also known as *chest tubes* or *thoracic drains,* are used to evacuate air or fluid or both from the pleural space. The reader is also referred to Chapter 31 for a discussion of thoracentesis. In many cases, tube thoracostomy can be lifesaving. The technique, however, requires familiarity with pulmonary and pleural anatomy and physiology. Indications, insertion technique, maintenance, and complications are discussed in this chapter.

32.3 INDICATIONS

The purpose of a chest tube is the removal of air or fluid from the pleural space in order to relieve pulmonary collapse and restore pleural subatmospheric pressure. Pneumothorax and pleural effusion are usually managed initially with thoracentesis, which can be repeated several times (see Chapter 31, Thoracentesis). Placement of a thoracostomy tube should be considered if repeated thoracentesis is required for ongoing air leakage or fluid production, if thoracentesis is insufficient for the severity of the disease (e.g., tension pneumothorax), if ongoing fluid production is expected (e.g., chylothorax), if suction as well as lavage is planned (e.g., pyothorax), or following thoracic surgery (Box 32-1).[2-6]

In the unstable patient with ongoing pneumothorax or pleural effusion, there are no absolute contraindications to thoracostomy tube placement. Relative contraindications in stable patients are coagulopathies or pleural adhesions.[2]

32.3.1 Box 32-1 Indications for Chest Tube Placement

- Tension pneumothorax
- Ongoing air leakage despite repeated thoracentesis
- Pyothorax
- Chylothorax
- Penetrating chest injury
- After thoracic surgery
- Performance of pleurodesis

32.4 THORACOSTOMY TUBE PLACEMENT

32.4.1 Material

There are numerous commercially available thoracostomy tubes. They come in various sizes and materials. Each has its advantages and disadvantages regarding material, price, and tissue compatibility.[7]

Thoracostomy tubes are commercially available as single tubes and complete thoracostomy kits. Other tubes can be modified to perform as thoracostomy tubes; however, several criteria must be fulfilled. The tube must be sterile, elicit minimal tissue reaction in situ, have multiple fenestrations at the distal end, and be able to withstand the generation of negative pressure during suctioning without collapsing.[8-10] A radiopaque line along the tube helps localize its position on radiographs. Most commercially available chest tubes come with a stylet to aid insertion into the pleural space and may have an open or closed end.

Adapters such as Christmas tree connectors, tubing with a Luer-Lok, a noncollapsing extension set, and a three-way stopcock are used to connect the tube to the suction device. It is advisable to have a tube thoracostomy set available in the ready area of the hospital (Box 32-2).[2]

A key to chest tube size selection is the flow rate of either air or liquid that can be accommodated by the tube.[7] This depends on the diameter and length of the tube and viscosity and rate of formation of the fluid. In humans, chest tube size is selected based on the type of lung disease and whether mechanical ventilation is required. Pleural drainage catheter flow capabilities vary significantly.[7]

Generally chest tube size is chosen with consideration of the nature of the pleural disease and the width of the patient's intercostal space. An unnecessarily large chest tube is likely to be associated with increased pain and discomfort. Aspiration of pleural effusion, especially pyothorax, generally is aided by a larger tube diameter in 134 order to remove 135 clots, cell debris, and fibrin, but thoracostomy tubes for drainage of a pneumothorax do not need to be of maximal diameter.

32.4.1.1

Box 32-2 Tube Thoracostomy Emergency Set

- Instrument set with hemostat, straight Kelly or Carmalt clamp, forceps, needle holder, scalpel holder, suture scissors
- No. 10 and 15 scalpel blades
- Two 30-cm extension sets
- Two three-way stopcocks
- Christmas tree adapters, two of each size
- 20- and 50-cc syringes, one of each
- Thoracostomy tube of appropriate size
- Sterile gauze
- Antibiotic ointment
- 3-0 and 1-0 monofilament suture

32.4.2

Anesthesia

Patients requiring chest tube placement should be supplemented with oxygen and be preoxygenated for anesthesia induction.[2] Analgesia is maintained by infiltration of a local anesthetic at the site of insertion, a regional nerve block, or by general anesthesia including analgesics.[10] Animals can be sedated, however the author prefers general anesthesia with the animal intubated in order to control ventilation and oxygenation. A rapid induction protocol is recommended[10] (see Chapters 162 and 163, Sedation of the Critically Ill Patient and Anesthesia of the Critically Ill Patient, respectively). If possible, thoracentesis under local anesthesia is performed before chest tube placement to make the animal a better anesthesia candidate.

Before sedation or anesthesia is administered, all materials should be ready and the chest wall should be clipped if the animal will tolerate it with minimal stress. Maintaining sternal recumbency during the procedure may be necessary to avoid respiratory compromise.

32.4.3

Techniques

Thoracostomy tube placement can be classified as either closed or open.[11] The key point in placement is the generation of a subcutaneous tunnel between the skin incision and the point of entry into the pleural space to create an airtight seal around the tube.[8]

Strict aseptic rules are required with all techniques.[1] The lateral thorax is clipped from behind the scapula to the last rib and surgically prepared. The animal ideally is placed in lateral recumbency, pending sufficient ventilation and oxygenation in this position. Once the area is prepared and appropriate anesthesia or analgesia has been provided, the area is draped. The material including tube, adapter, and suction device and a small surgery pack should already be prepared.

Several techniques for closed placement of a chest tube exist.[2,8,9,11,12] The author prefers the following (Color Plate 32-1).[8,12] The skin over the lateral chest is pulled cranially by an assistant. While the skin is held in this position the appropriate intercostal space is identified, usually the seventh, eighth, or ninth. The length of tube to insert into the thorax is estimated at this time by holding the chest tube along side the chest with the tip aligned to the second rib, without compromising sterility. A small skin incision, slightly larger than the diameter of the tube, is made overlying the desired intercostal space midway between the dorsal midline and the center of the lateral thorax. The subcutaneous tissue and muscle layers are bluntly dissected with a hemostat. The pleura is then penetrated bluntly using a large hemostat or Carmalt forceps (see Color Plate 32-1, *A*). During this maneuver, the anesthetist is asked to stop ventilation in order to minimize injury to the lung.[13] Also, injury to the underlying organs is minimized by holding the hemostat close to the tip with the nondominant hand to avoid overpenetration.

Once the pleura is penetrated, the tips of the hemostat are opened, thereby creating an opening for the thoracostomy tube (see Color Plate 32-1, *B*). Before insertion, the trochar can be retracted slightly so that the sharp tip is protected by the tube. The tip of the tube is introduced into the thorax and is then advanced toward the uppermost elbow. Once the tip of the tube is well inside the thorax, the hemostat can be removed. The thoracostomy tube should be inserted so that the tip is roughly at the level of the second rib. It is essential that all tube fenestrations are within the thoracic cavity.[2] The stylet is then withdrawn and the hemostat or a tube clamp can be used to clamp the tube off.

Alternatively, the tube is connected directly to the suction device. As the skin is released and retracts caudally over the tube, a subcutaneous tunnel is created. The Mac technique can be used to rule out kinking of the tube: the tube is twisted 180 degrees in each direction and then released. If the tube spins back into its position, this is indicative of kinking.[14] Depending on the urgency for pleural evacuation, suction is instituted prior to or after securing the tube. A purse-string suture is placed around the skin incision if the fit is not firm. The tube is then fixed using a finger-trap suture pattern.[15] A single interrupted suture is placed through the skin at the site of insertion. This suture may pass through the periosteum of the rib (this requires additional local anesthetic) and is tied in a gentle loop, leaving equal and long suture tags. The sutures tags are used to perform the finger trap by placing a single knot on top of the tube, then crossing underneath the tube followed by another single knot on top of the tube and so on. After four to six finger traps, the tube is once more anchored to the skin, therefore minimizing the chance of dislocation (see Color Plate 32-1, *C*). The tube is then connected to the suction system of choice.

Antibiotic ointment is applied to the insertion site and the area is covered with sterile gauze. A bandage is applied to secure the thoracostomy tube to the chest wall and minimize risk of accidental removal.[8]

If no assistant is available to pull the skin forward, the subcutaneous tunnel can be made with a large hemostat or Carmalt forceps. The skin incision is made more caudally (eighth to tenth intercostal space), and the hemostat is tunneled cranially through the subcutaneous tissues' two intercostal spaces, to the desired insertion point at the level of the sixth to eighth intercostal space. At this point, the pleural space is entered and the tube is inserted as described earlier.[2,11]

A thoracostomy tube with a sharp-ended stylet can be placed without the aid of a hemostat[11]; however, the technique of perforating the pleura by punching the distal end of the stylet is not recommended because of increased risk of injury to intrathoracic organs. A combination of blunt dissection through the intercostal space with hemostats and penetration of the pleura with the stylet is preferable.

An alternative for thoracostomy tube placement is the Seldinger technique.[2] The tube is inserted into the thorax with the use of a guidewire that has been inserted through a small needle. After removal of the needle, the guidewire stays in place and the modified tube is advanced over the wire. Once the tube is placed, the guidewire is removed and the tube is secured as described above. Care is taken not to compromise the lumen of the catheter with the finger-trap suture. The Seldinger technique has the advantage of a smaller incision and might therefore be less painful and leakage less likely.

Open insertion of a thoracostomy tube is performed during thoracotomy, with the advantage that the tube is placed safely under direct visualization. Under certain circumstances, such as when an animal has an open penetrating chest injury, a thoracostomy tube can be inserted directly into the thoracic cavity through the wound. The wound is then sealed with nonadhesive dressing and the thorax is evacuated immediately. Proper wound debridement and lavage and placement of a new and sterile thoracostomy tube are required as soon as the patient is stable enough for anesthesia.

32.5 DRAINAGE

After placement of a thoracostomy tube, negative pressure is generated by manual aspiration or a continuous suction apparatus. The smallest number of connections should be used because they are potential sites for leaks. Cable ties are recommended to secure all connections. Too much negative pressure should be avoided because it can lead to lung tissue trauma and occlusion of the tube by mediastinal or pleural tissue. The normal difference between the pleural pressure and the intraalveolar pressure is 4 to 8 mm Hg, which translates to 5 to 10 ml of vacuum in a syringe.[11]

Thoracic radiographs are recommended to confirm proper tube placement, evaluate expansion of the lung, and identify residual pleural fluid or air.[2] Tubes that are kinked or tubes that are not placed between the chest wall and the lung should be partly removed and redirected (only if sterility will not be compromised). Insertion as far as the thoracic inlet might cause extensive pain, and in this case the tube should be pulled back to the level of the second rib.

Further drainage is accomplished using either intermittent or continuous suction. The method used depends on the nature of the pleural space disease and the availability of equipment.[2,8,16,17] In veterinary patients, intermittent manual syringe aspiration every 1 to 6 hours is sufficient in many cases and allows for adequate drainage and maintenance of negative pleural pressure.[11]

32.5.1 Passive Drainage Techniques

Passive drainage of the pleural space relies on the increased intrathoracic pressure generated during exhalation in a spontaneously breathing patient to force air or fluid from the pleural space. Alternatively, in patients receiving positive-pressure ventilation pleural drainage will occur during the inspiratory phase. These techniques generally are not as effective as active drainage and are more suited to mild pleural space disease. Interestingly, in one human study passive drainage following thoracoscopy for spontaneous pneumothorax led to more rapid recovery than active thoracic drainage techniques.[18] Human patients usually are more comfortable with passive drainage than with active drainage. Passive drainage is also enhanced by keeping the patient higher than the drainage apparatus; this may not be possible in larger veterinary patients.

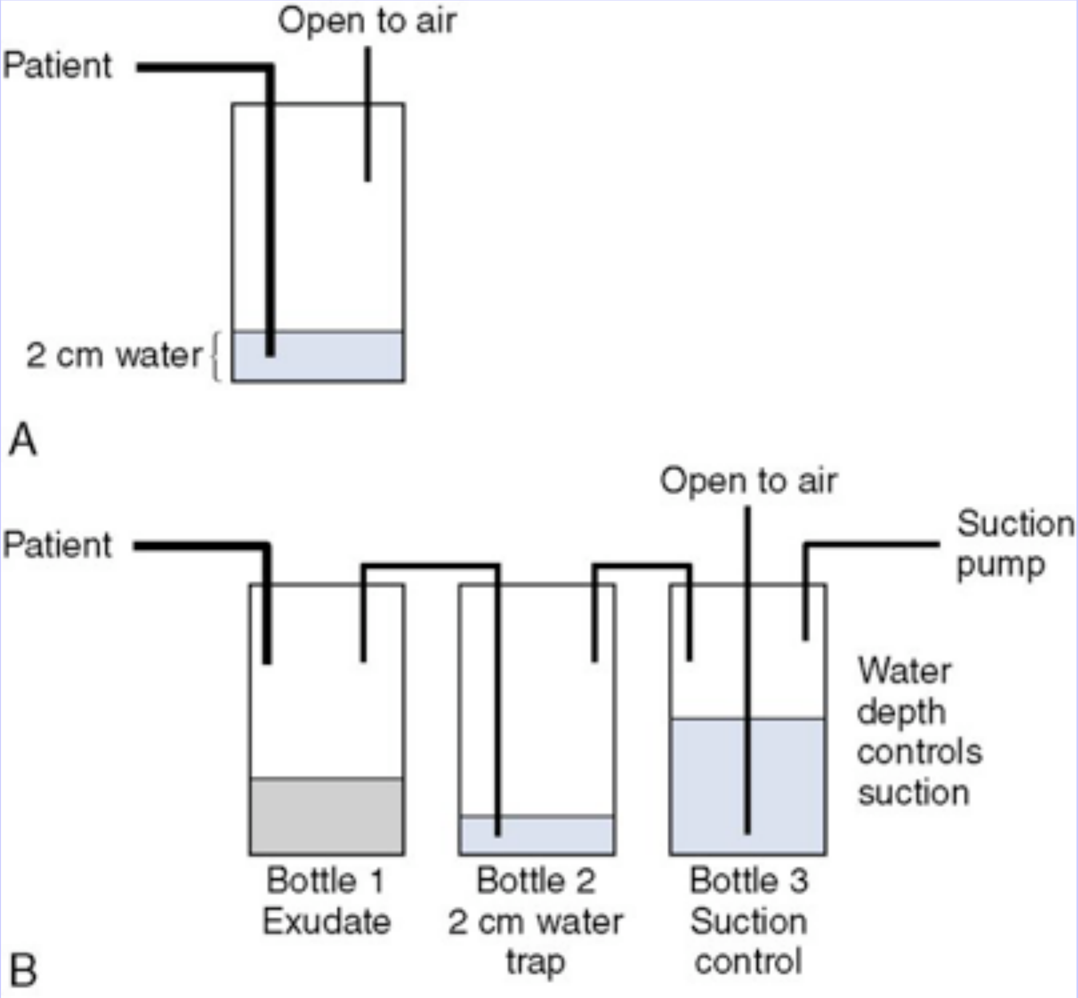
Passive drainage can be achieved with a simple one-bottle water seal (Figure 32-1, *A*) or with a Heimlich valve. Heimlich valves are one-way flutter valves that can be attached to chest tubes to allow pleural air to be expelled during exhalation (if breathing spontaneously) but prevent entrainment of air into the pleural space during inspiration.[2] They provide a simple and inexpensive option for drainage but are effective only in the management of relatively mild pneumothoraces and are prone to malfunction. The Heimlich valve can be occluded readily by secretions, which may be a life-threatening complication, and requires constant monitoring.

32.5.2 Active Drainage Techniques

With continuous air leaks or severe fluid accumulation, continuous active suction may be necessary. Continuous suction may also allow sustained lung expansion and better healing of leaks by pleural adhesion. Continuous suction requires a water seal between the suction pump and the chest tube; this can be achieved with a two-chamber or three-chamber suction apparatus.[2] In connecting chest tubes to a suction system the smallest number of connections should be used because they are potential sites for leaks. Cable ties are recommended to secure all connectors.

The three-chambered, waterseal suction apparatus is recommended. These are commercially available or can be constructed with three bottles (Figure 32-1, *B*).[2,17] A suction pressure of 10 to 20 cm H_2O is used.[2,9] This is 136 achieved by filling the third chamber (connected directly to the suction pump) with water to a depth of 10 to 20 137 cm. The central chamber is the water seal, which is achieved by submerging the tubing entering the second bottle in 2 to 3 cm of water. The first chamber is connected to the chest tube and collects fluid aspirated from the thorax. Pleural effusion can be quantitated by measuring the fluid accumulation in the first chamber, while ongoing air production from a pneumothorax is evidenced by bubbles in the central water seal container. With persistent air leakage, continuous suction may be necessary for several days. If intrapleural air continues to accumulate after more than 2 to 5 days, surgical exploration of the thoracic cavity may be indicated.[2,6,19]

Figure 32-1 **A,** Single-bottle suction apparatus. This single-bottle system acts both as a water seal and a collection chamber so that the depth of liquid may increase with time, which will reduce effective drainage. This system is for passive drainage only. Bubbling is evidence of air drainage from the pleural space. **B,** Three-bottle suction apparatus. The three-bottle system has a collection bottle, a water trap, and suction control bottle. It allows regulation of suction level by changing the water depth in bottle 3. There is a water seal so that suction can be turned off without concern of air leaking back into the pleural space. The exudates in bottle 1 can be evaluated and emptied independently. The water trap will bubble if air is evacuated from the pleural space.



If at any time negative pressure cannot be achieved despite continual aspiration, the tubing should be checked for air leaks, and all adaptors and three-way stopcocks should be checked and replaced in a sequential manner.

32.6 MAINTENANCE AND CARE

Strict aseptic care is required. Antibiotic prophylaxis is controversial and depends mostly on the circumstances in which the tube was placed and the animal's underlying disease.[1,20] Prophylactic antibiotics may be indicated in people if thoracostomy tubes are placed because of chest trauma.[21] Thoracostomy tubes increase the risk of nosocomial infections after thoracic surgery in humans.[22]

Bandages should be changed at least daily, and tubing should be wrapped to prevent accidental removal by the animal. A tubing clamp can be placed in addition to the 3-way stopcock if the tube is not being aspirated. It is essential that the animal be prevented from damaging the tube, and an Elizabethan collar may be required in some cases.

Animals with thoracostomy tubes need 24-hour monitoring. Respiratory rate and effort are checked on a regular basis, and other vital parameters are monitored based on the patient's problem(s). Analgesia is best provided by a combination of intravenous analgesia and administration of local anesthetics through the chest tube (see Chapter 164, Analgesia and Constant Rate Infusions).

32.7 REMOVAL

The decision to remove a chest tube depends on the rate of fluid production or air accumulation in the pleural space. As a general guideline, no air should be retrieved for 24 hours before tube removal. Tube removal can be considered if fluid production falls to less than 2 ml/kg per 24 hours.[8] In humans, thoracostomy tubes are removed if daily fluid aspiration is less than 150 to 200 ml.[2,23] Exemptions are septic exudates and the use of the thoracostomy tube as a device for lavage. Dogs with spontaneous pneumothorax requiring chest tubes have them for an average of 4.5 days (range 1 to 8 days).[11,24]

Thoracic radiographs are recommended before tube removal to ensure that the pleural space disease has truly been resolved. Tube occlusion or displacement can lead to negative aspiration results despite persistent pleural space disease.[2] Studies in humans recommend routine chest radiographs after thoracostomy tube removal only if clinical signs of respiratory distress are identified.[25]

For removal, the tube is smoothly and rapidly removed and a nonadherent pad with antibiotic ointment is pressed firmly over the exit site. A light bandage is applied and the incision is allowed to heal by second intention.

32.8 COMPLICATIONS

The most common complication of percutaneous thoracostomy is improper placement.[26] Other complications include hemorrhage, infection, visceral injury, and reexpansion pulmonary edema.[27] In human medicine, the complication rate is between 20% and 30% and depends on the experience of the operator.[28,29]

32.9 SUGGESTED FURTHER READING*

DT Crowe, JJ Devey: Thoracic drainage. In MJ Bojrab (Ed.): *Current techniques in small animals*. 1997, Williams & Wilkins, Baltimore, *One of the most extensive textbooks describing thoracostomy tube placement in small animals. Includes nice illustrations and an extensive discussion*.

TD Kirsch, P Mulligan: Tube thoracostomy. In JR Roberts, JR Hedges (Eds.): *Clinical procedures in emergency medicine*. 2004, Saunders, Philadelphia, *The state-of-the-art description of thoracostomy tube placement in human medicine. Recommended for an in-depth discussion on thoracostomy tube placement. Includes a detailed description of the Seldinger technique*.

DM Tillson: Thoracostomy tubes. Part I. Indications and anesthesia. *Compend Contin Educ Pract Vet*. **19**, 1997, 1258, *Very nice review regarding indications, anatomy, types of tubes, and anesthesia for thoracostomy tube placement. Contains a description of a self-made chest tube. Easily readable while very informative*.

DM Tillson: Thoracostomy tubes. Part II. Placement and maintenance. *Compend Contin Educ Pract Vet*. **19**, 1997, 1331, *Second part of this extensive review article including several techniques for placement and description of continuous suction drainage in veterinary patients*.

GA Watson, BG Harbrecht: Chest tube placement, care, and removal. In MP Fink, E Abraham, JL Vincent, PM Kochanek (Eds.): *Textbook of critical care*. 2006, Saunders, Philadelphia, *The human "bible" of critical care medicine containing an extensive chapter about troubleshooting and management, including the guidelines for thoracostomy tube management in human patients. Reader referred to veterinary textbooks regarding thoracostomy tube placement*.

* See the CD-ROM for a complete list of references

33 Chapter 33 Chest Wall Disease

Suzanne Donahue, VMD, DACVECC

33.1 KEY POINTS

- The chest wall is necessary for respiration and protection of the thoracic cavity.
- Diseases of the chest wall include congenital anomalies, neoplasia, trauma-induced abnormalities (rib fractures, flail chest, penetrating wounds), cervical spine disease, and neuromuscular disease.
- The history and physical examination can usually establish a diagnosis of chest wall disease. Thoracic radiographs may also be informative.
- Initial treatment is aimed at stabilizing the patient and providing mechanical ventilatory assistance if indicated. Medical or surgical management of underlying diseases may be necessary.

33.2 INTRODUCTION

Diseases of the chest wall must always be a differential for diagnosis of respiratory distress. Often a thorough history and physical examination will help to confirm a diagnosis and ensure appropriate and timely therapy.

33.3 CHEST WALL ANATOMY AND FUNCTION

The chest wall has two main functions. The bones of the chest wall (thirteen pair of ribs, thirteen vertebrae, and nine sternebrae) serve to protect the internal structures of the thorax. The muscles of the chest wall (mainly the diaphragm and the external and internal intercostal muscles), and the nerves that innervate them, are necessary for normal respiration to occur.

When the diaphragm is stimulated, it contracts and moves caudally in animals. At the same time, the intercostal muscles move the rib cage cranially and outward. When the chest wall moves outward, the lungs are “pulled” with it as negative pressure is generated within the pleural space. As the intrathoracic volume increases during inspiration, the pressure within the alveoli decreases slightly. Airway pressure becomes lower than atmospheric pressure, which causes air to flow into the lung. When the diaphragm and intercostal muscles relax during expiration, the elastic recoil of the lungs and chest wall compresses the lungs and expels the air. During heavy breathing, the abdominal muscles also assist with exhalation.

33.4 DIAGNOSIS OF CHEST WALL DISEASE

Diagnosis of chest wall disease is based mainly on history and physical examination. A hallmark of chest wall disease with a component of respiratory muscle paralysis is a paradoxical breathing pattern. This is characterized by decreased chest wall movement and inward movement of the abdominal wall during inspiration instead of the normal outward movement. Radiographs may be helpful when certain disease processes are suspected (rib fractures, congenital deformities, or neoplasia). Lastly, arterial blood gas changes indicating hypoventilation can also provide evidence of chest wall disease. In general, an arterial partial pressure of carbon dioxide ($PaCO_2$)

greater than 50 mm Hg is evidence of hypoventilation that may be due to several disease processes, including chest wall disease.

33.5 DISEASES OF THE CHEST WALL

33.5.1 Congenital

Congenital disease of the chest wall is rare. The most common abnormality is pectus excavatum, an inward concavity of the sternum and costal cartilages. Animals with this disease are often asymptomatic; however, respiratory distress can occur via either "restrictive ventilation or paradoxical movement of the deformity during inspiration."[1] Surgical management is indicated only if there is significant respiratory impairment.

33.5.2 Neoplasia

Neoplasia of the chest wall, although fairly common, does not often lead to respiratory distress. The main concern is whether the mass is benign or malignant. A biopsy is needed to determine treatment options. Common masses of the chest wall include lipoma, chondrosarcoma, osteosarcoma, fibrosarcoma, mast cell tumor, and hemangiosarcoma.[1] Surgical management, including aggressive resection, movement of the diaphragm cranially, mesh placement, or flap procedures may be necessary and may lead to respiratory difficulties postoperatively, especially in animals that require one or more concomitant lobectomies. Pain control is an important part of patient treatment in these cases (see Chapter 164, Analgesia and Constant Rate Infusions).

33.5.3 Rib Fractures

33.5.3.1 Trauma

Rib fractures are often significant from the standpoint of pain management. The patient may hypoventilate if severe discomfort is present during respiration. Although rib fractures do not routinely require stabilization, their presence should alert the clinician to the possibility of underlying soft tissue thoracic injury, including pulmonary contusions, diaphragmatic hernia, hemothorax, and/or pneumothorax. If the rib fractures are very unstable, they can cause further trauma to the surrounding tissues and intrathoracic structures (i.e., lungs), thus necessitating surgical intervention.[2]

33.5.3.2 Flail Chest and Intercostal Muscle Damage

Flail chest is defined as a "fracture of several adjoining ribs resulting in a segment of thoracic wall that has lost continuity with the rest of the hemithorax."[2] This results in the fractured segment moving paradoxically throughout respiration. During inspiration, as the chest wall moves outward, the flail segment collapses inward due to negative intrapleural pressure and vice versa.[2]

Respiratory distress often occurs in patients with flail chest. There are two are reasons for this. First, patients can hypoventilate purely because of pain. Second, many animals with flail chest have other lung injuries, such as pneumothorax, hemothorax, pulmonary contusions, or a diaphragmatic hernia, which can increase the degree of hypoxemia.

Management of flail chest can be purely medical or a combination of medical and surgical. Initially, the patient should be laid down on the side with the flail segment, or the chest can be wrapped. This reduces bulging of the segment during exhalation (although it will still be pulled inward with inhalation) to minimize pain and secondary trauma. If ventilation is severely impaired, intubation and manual ventilation may be lifesaving in that it may ensure that a tension pneumothorax is not present before positive-pressure ventilation is initiated (see Chapter 213, Basic Mechanical Ventilation). Aggressive analgesia is often helpful, although the animal should be monitored closely for respiratory depression and mechanical ventilation provided if necessary (see Chapters 164 and 213, Analgesia and Constant Rate Infusions and Basic Mechanical Ventilation, respectively).

Time and cage rest are often the treatment of choice. An external stabilization splint, which covers the affected and unaffected surrounding areas and is sutured to the chest wall, has been used to provide chest wall support. Whether or not to surgically stabilize the flail chest segment is controversial. Often the actual flail segment contributes very little to dyspnea, hypoxemia, or hypoventilation, and pain or coexisting disease is the primary cause of these abnormalities. However, surgically stabilizing the segment reduces pain and improves thoracic wall excursion and ventilation, and should be performed if anesthesia and surgery are required for other reasons. If the flail segment is displaced or adding to further lung dysfunction (laceration of the lung or vasculature by the flail segment), surgery is necessary (see Chapter 153, Thoracic Trauma).

Tearing of the intercostal muscles secondary to fractured ribs or a penetrating injury may cause a loss of chest wall rigidity and paradoxical movement of the affected area or flail segment. The degree of ventilatory impairment depends on the size of the destabilized area. This condition rarely causes direct respiratory impairment, but rather leads to pain and may be a sign of additional injuries.

33.5.3.3 Penetrating Wounds

If penetrating chest wall injuries allow air to enter into the pleural space, an open pneumothorax will develop. This should be closed manually to create an airtight seal and a chest tube should be placed, either at the site of the wound or a different location, in order to remove the air and reestablish negative pressure in the pleural space. A liberal amount of sterile ointment and an occlusive chest wrap can be used to cover the wound and maintain an airtight seal. As soon as the patient is stabilized, debridement and surgical repair should be performed. It is very important to monitor these patients closely because other internal organs could easily have been damaged as well, leading to continued pneumothorax, hemothorax, diaphragmatic hernia, or pulmonary contusions (see Chapter 153, Thoracic Trauma).

33.5.4 Cervical Spine Disease

Cervical spine diseases, such as cervical spine fractures or intervertebral disk disease, can cause significant hypoventilation. The exact mechanism is unknown, although there are many potential contributing factors. In dogs, the medullary respiratory center sends information via the reticulospinal tracts to the phrenic nerve and the segmental intercostal nerves. The phrenic nerve leaves the spinal cord between the fourth and sixth vertebral bodies and provides motor innervation to the diaphragm. The segmental intercostal nerves innervate the intercostal muscles and leave the spinal cord between C1 and T2. If these pathways are disrupted, ventilatory failure can ensue.[3] In cats, there is some evidence that afferent tracts to the respiratory center may be damaged during surgery on the cervical spine.[4]

33.5.5 Tick Paralysis

33.5.5.1 Neuromuscular Disease (see Chapter 101, Lower Motor Neuron Disease)

Tick paralysis is induced when an engorged female tick secretes a neurotoxin into the patient that either inhibits depolarization of motor nerves or blocks the release of acetylcholine. In the United States, the ticks most frequently involved are the American dog tick *(Dermacentor variabilis)* and the Rocky Mountain wood tick *(Dermacentor andersoni)*.[5] Signs typically develop 1 week after attachment of the tick. Patients often demonstrate marked ataxia of all four limbs, which progresses quickly to tetraparesis with generalized lower motor neuron symptoms. For an unknown reason, cranial nerve involvement is rare in the United States. If the tick is not found and removed, patients can progress to respiratory failure and ultimately death. Diagnosis is often made upon cessation of signs following tick removal. This often occurs within 24 hours, with a complete recovery by 72 hours.[5] If tick paralysis is suspected, but no ticks are found, rapid-acting insecticide solutions should be applied to the patient.

33.5.5.2 Acute Idiopathic Polyradiculoneuritis

Acute idiopathic polyradiculoneuritis, also known as coonhound paralysis, is seen primarily in hunting dogs that presumably have been exposed to raccoons, but it also has been seen in dogs with no raccoon exposure.[5] The disease occurs via immune-mediated demyelination and degeneration of axons of the ventral roots and spinal nerves.[5] This leads to an effective blockade of motor signals from the spinal cord to the muscles.

Clinical signs begin with pelvic limb paresis and hyporeflexia and can progress to tetraparesis within several days. The clinician will often detect diffuse hyperesthesia. If the disease is rapidly progressive, the patient may develop respiratory paralysis. Cranial nerve involvement is uncommon with coonhound paralysis. The clinical course tends to be approximately 3 to 6 weeks but can be significantly longer. Improvement usually begins by the third week.[5]

Diagnosis is based mainly on clinical suspicion. Coonhound paralysis is suspected when tick paralysis and botulism can be ruled out. The diagnosis can be supported by electromyelographic evidence of diffuse denervation of affected muscles.[5] Management is supportive and may be prolonged in severe cases. The prognosis is typically good if complications are prevented, but recurrences have been described.

33.5.5.3 Botulism

Botulism is seen when the preformed *Clostridium botulinum* toxin is ingested. There are several types of botulism toxin, but all cases reported in dogs have been the result of type C toxin,[5] which is known to inhibit the release of acetylcholine from nerve terminals.

Clinical signs occur within 1 week of ingestion. These include mild generalized weakness or, in more severe cases, tetraparesis and possible respiratory failure. Unlike coonhound paralysis, cranial nerve deficits can be seen with botulism. Duration of the disease is usually less than 2 weeks.[5]

Diagnosis is confirmed only by identification of the toxin in the serum, feces, or vomitus of the patient, or in the food or carrion that the patient ingested. Electromyelography may help to differentiate botulism from coonhound paralysis, but it is not definitive.

As for the other lower motor neuron diseases, management is largely supportive. There is an antitoxin available, but it needs to be administered before the toxin binds to receptors, which is not often possible.[5] Efficacy of antibiotics to manage *Clostridium* is unknown. Prognosis is generally good with aggressive supportive care and prevention of complications (e.g., aspiration pneumonia).

33.5.5.4 Fulminant Myasthenia Gravis

Myasthenia gravis occurs most commonly due to an autoimmune block, alteration, or destruction of the acetylcholine receptors at the neuromuscular junctions, but it can also be due to a congenital decrease in the number of these receptors on the postsynaptic membrane. Physical examination often reveals normal neurologic findings in the resting animal. With exercise, muscle weakness becomes apparent and will worsen with continued exertion. The limbs are most grossly affected. Evidence of regurgitation with or without aspiration pneumonia secondary to megaesophagus commonly is present.

A presumptive diagnosis is made based on exercise-induced weakness, a decreasing response to repetitive nerve stimulation, or a positive response to acetylcholinesterase drugs such as edrophonium.[5] A definitive diagnosis is made when acetylcholine receptor antibodies are detected in the serum. Muscle biopsy with special staining is also used to diagnose congenital myasthenia gravis.

Management entails the use of an anticholinesterase agent like pyridostigmine and, often, glucocorticoids (see Chapter 101, Lower Motor Neuron Disease). Management with azathioprine and mycophenolate mofetil has also proven useful and may minimize side effects of steroid administration.Thymectomy has also been described for patients that respond poorly to medical management, because thymoma has been found to cause myasthenia gravis.[5]

33.5.5.5 Coral Snake Envenomation

Bites from the coral snake *(Micrurus fulvius fulvius)* also lead to lower motor neuron disease. The venom from these snakes contains neurotoxic components, which leads to neuromuscular blockade. Clinical signs develop rapidly and, unfortunately, there is usually minimal to no local tissue reaction as is seen with other snake bites. Signs range from peripheral weakness to tetraparesis. In severe cases, paralysis of respiratory muscles occurs. Patients may or may not have signs of hemolysis.[6]

Management is mostly supportive, although antivenin can be used early in the disease process. Unfortunately, once signs are evident, efficacy of antivenin diminishes rapidly (see Chapter 101, Lower Motor Neuron Disease).[6]

33.6 SUGGESTED FURTHER READING*

AS King: Autonomic components of the CNS. In AS King (Ed.): *Physiological and clinical anatomy of the domestic mammal*. 1987, Oxford University Press, Oxford, *A detailed review of the autonomic nervous system in animals*.

KA Kremer, M Schaer: Coral snake *(Micrurus fulvius fulvius)* envenomation in five dogs: present and earlier findings. *J Vet Emerg Crit Care*. **5**, 1995, 1, *A complete review of coral snake envenomation pathology and prognosis in small animal patients*.

AJ Krieger: Respiratory failure after ventral spinal surgery: a clinical and experimental study. *J Surg Res*. **14**, 1973, 512, *A description of the pathophysiology of respiratory failure following cervical injury*.

CM MacPhail: Thoracic injuries. In WE Wingfield, MR Raffe (Eds.): *The veterinary ICU book*. 2002, Teton NewMedia, Jackson Hole, WY, *A complete review of chest wall and pulmonary injuries in small animal patients presented in a concise manner*.

JE Oliver, MD Lorenz, JN Kornegay: Tetraparesis, hemiparesis, and ataxia. In MD Lorenz, JN Kornegay (Eds.): *Handbook of veterinary neurology*. ed 3, 1997, Saunders, Philadelphia, *An excellent review of the pathophysiology and management of lower motor neuron diseases in veterinary patients*.

EC Orton: Thoracic wall. In D Slatter (Ed.): *Textbook of small animal surgery*. ed 2, 1993, Saunders, Philadelphia, *A great in-depth look at the pathophysiology and management of surgical chest wall disease processes in veterinary patients*.

* See the CD-ROM for a complete list of references

34 Chapter 34 Nonrespiratory Look-Alikes

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34.1 KEY POINTS

- Respiratory distress, dyspnea, or tachypnea may occur as a result of disease processes not directly affecting the upper and lower airways, pulmonary parenchyma, pulmonary circulation, pleural space, and chest wall or diaphragm. Examples of nonrespiratory “look-alikes” (increased respiratory effort due to nonrespiratory causes) include respiratory compensation for metabolic acidosis, decreased oxygen content, pain, anxiety, stress, drugs, hyperthermia, hypovolemia, abdominal enlargement, metabolic derangements, and neurologic disease.
- Respiration is the only vital function with both automatic and voluntary components.
- The compensatory mechanism for metabolic acidosis is hyperventilation resulting in a respiratory alkalosis secondary to increased respiratory rate and depth.
- Decreased oxygen delivery to chemoreceptors due to a decrease in oxygen content (e.g., anemia, dysfunctional hemoglobin, pericardial tamponade, or a decrease in the partial pressure of oxygen in the plasma) or hypovolemia (e.g., decreased cardiac output) results in increased respiratory rate and depth.
- Pain, anxiety, and stress can affect the voluntary component of respiration, resulting in apparent dyspnea.
- When hyperthermia occurs, evaporative cooling via the respiratory tract results in tachypnea and a shallow breathing pattern.
- Disease processes affecting the nerves, muscles, or neuromuscular junctions to the intercostal muscles or diaphragm may result in an abnormal respiratory pattern.
- Brain lesions or drugs affecting areas that are responsible for respiratory signaling (e.g., medulla, cerebral cortex) will directly affect breathing rate and rhythm.
- Metabolic diseases, such as hyperadrenocorticism and hyperthyroidism, and severe biochemical derangements (e.g., potassium, calcium, glucose) affect the respiratory pattern as a result of altered respiratory mechanics, input to respiratory sensors, and compromise of respiratory muscles.
- Severe abdominal distention may cause pain, discomfort, decreased venous return to the heart, and metabolic acidosis, in addition to pushing the diaphragm cranially and inhibiting normal inspiratory movement.

34.2 INTRODUCTION

The “simple” job of the respiratory system, which is the delivery of oxygen to vasculature in the lungs and removal of carbon dioxide, is regulated by a complex system centered in the brain. The brain stem (medulla) generates signals transmitted to both the upper airway and main and accessory respiratory muscles to control the rate and pattern of breathing. Modification of the respiratory rate and pattern can be accomplished via afferent feedback from mechanoreceptors in the lung, airway, diaphragm, and chest wall, as well as chemoreceptors (monitoring pH and partial pressures of carbon dioxide [PCO_2] and oxygen [PO_2]) located centrally and peripherally. Additionally, the cortex and subcortex (supramedullary regions) can affect respiratory rate and pattern with volition, emotion, and onset of exercise.[1,2] In other words, respiration is the only vital function that has both an automatic (brain stem) and a voluntary (cortical) component.[3]

Because of the extensive network of input that can affect respiratory rate and pattern, patients with disease processes not directly affecting the upper and lower airways, pulmonary parenchyma, pulmonary circulation, pleural space, or chest wall may present with clinical signs of respiratory distress, dyspnea, or tachypnea. This becomes important to the veterinarian because patients with respiratory difficulty should be evaluated for both respiratory disease and nonrespiratory "look-alikes." Specific nonrespiratory look-alikes include respiratory compensation for a metabolic acidosis, a decrease in oxygen content (e.g., anemia, dysfunctional hemoglobin), pain, anxiety, stress, drug-induced difficulties, hyperthermia, hypovolemia, abdominal enlargement, metabolic disease, and neurologic disease. A concise history from the owner, a thorough physical examination, and appropriate diagnostic techniques should all be used concurrently to differentiate respiratory system disease from these nonrespiratory look-alikes. Multiple concurrent disease processes are common.

34.3 pH and pCO_2 RECEPTOR ACTIVATION

The most common acid-base abnormality in small animals is metabolic acidosis.[4] Metabolic acidosis is characterized by an increased hydrogen ion concentration, decreased pH, and decreased bicarbonate ion (HCO_3^-) concentration (see Chapter 59, Acid-Base Disturbances).[5] Metabolic acidoses most often result from a loss of bicarbonate-rich fluid from the body, increased hydrogen ion production, or decreased renal hydrogen ion excretion. In small animal medicine, the more common processes that cause metabolic acidoses are diabetic ketoacidosis, diarrhea-induced hyperchloremic acidosis, lactic acidosis, and uremic acidosis.[5] The normal compensatory mechanism for metabolic acidosis is to expel additional carbon dioxide via hyperventilation, as evidenced by a decrease in the partial pressure of carbon dioxide in the peripheral arterial blood ($PaCO_2$). This compensatory mechanism is initiated as a result of the increased number of hydrogen ions stimulating peripheral and central chemoreceptors, which in turn increases alveolar ventilation (hyperventilation).[5]

Canine patients with metabolic acidosis disorders may demonstrate increased respiratory depth and rate reflecting an attempt to normalize systemic pH by blowing off carbon dioxide. The expected compensatory respiratory response is a decrement in $PaCO_2$ by 0.7 mm Hg per 1 mEq/L decrease in plasma bicarbonate concentration.[5] Although data are limited, this respiratory compensation is less commonly observed in cats.[6]

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Respiratory compensation may result in characteristic patterns such as Kussmaul respirations seen with diabetic ketoacidosis; this is clinically recognized as a deep, rhythmic breathing pattern.[5] Although this may not be classically seen in veterinary medicine, compensatory hypocapnia should be differentiated from underlying lung disease in these patients.

34.4 pO_2 RECEPTOR ACTIVATION

Oxygen-sensing receptors located in the carotid and aortic bodies are stimulated to increase respiratory rate and depth when inadequate oxygen is delivered to their sites. Under normal circumstances, central respiratory drive is modified primarily by changes in arterial PCO_2, which leads to an increase in the hydrogen ion concentration.

However, hypoxemia becomes the primary stimulation for ventilation when the partial pressure of oxygen in the peripheral arterial blood drops below 50 mm Hg (PaO_2 <50 mm Hg).[7]

Recall that the formula to determine arterial oxygen content (CaO_2) is:

$CaO_2 = (Hg \times SaO_2 \times 1.34) + 0.003 \times PaO_2$ and for oxygen delivery (DO_2) is:

$DO_2 = CaO_2 \times CO$ where Hg is the hemoglobin concentration (g/dl), SaO_2 is the percent oxyhemoglobin saturation of arterial blood, PaO_2 is the partial pressure of oxygen in the arterial blood (mm Hg), and CO is cardiac output (dl/min).[7]

Patients with anemia, hypovolemia, pericardial tamponade, or other types of blood flow obstruction (e.g., severe abdominal distention with gastric dilatation-volvulus) may appear tachypneic in an attempt to increase oxygen delivery. A decrease in oxygen delivery to chemoreceptors in the carotid and aortic bodies will stimulate an increase in respiratory rate and depth in order to deliver more oxygen to the alveoli for gas exchange. Clinically, this increase in respiratory rate and effort may result in a decrease in $PaCO_2$, even with coexisting pulmonary parenchymal disease, because carbon dioxide is 20 times more diffusible than oxygen, and is characterized by a steep dissociation curve.[7] Anemia, whether from decreased production, blood loss, destruction, or sequestration, will significantly affect oxygen-carrying capacity and the delivery of oxygen to PO_2 chemoreceptors. In animals with acute blood loss, cardiac output is increased in an attempt to increase oxygen delivery by increasing heart rate and stroke volume; this is seen clinically as signs of hypovolemic shock. In chronically anemic patients, compensation occurs via increases in cardiac output or changes in the affinity of hemoglobin for oxygen.[8]

Patients with altered hemoglobin-oxygen binding, including methemoglobinemia (e.g., acetaminophen toxicity) or carboxyhemoglobinemia (e.g., carbon monoxide poisoning, smoke inhalation), will have a decreased SaO_2. It is important to recognize that pulse oximetry is inaccurate with dysfunctional hemoglobin.

Finally, patients with underlying heart disease may have an increased respiratory rate and altered respiratory pattern due to a decrease in cardiac output. Clinically this should be distinguished from primary respiratory disease (e.g., pleural effusion, pulmonary edema), which may also be present. In summary, patients with decreased oxygen delivery from either anemia or hypovolemia may have a component of tachypnea or dyspnea from carotid and aortic receptor stimulation or from simultaneous anatomic respiratory disease.

34.5 CORTICAL MODIFICATION OF RESPIRATION

Dyspnea, the term used to characterize a subjective experience of breathing discomfort, may have a cyclic component when related to pain, stress, or anxiety.[3] The voluntary (cortical) component of respiratory control can be altered in situations that cause pain, stress, or anxiety (e.g., severe abdominal enlargement). Sympathetic stimulation (fight or flight) from pain, stress, or anxiety may result in hyperventilation and apparent dyspnea. The sympathetic response helps prepare the animal for immediate action by increasing oxygen delivery to the tissues and removing carbon dioxide generated with increased muscle activity.[9] When physical activity (fighting or escaping) does not occur, additional anxiety may result in hyperventilation.

Additionally, pain may limit chest expansion and cause anxiety, which may further increase respiratory distress (e.g., flail chest). Changes in the brain and spinal cord neurons result in central sensitization or a heightened perception of pain.[10] As a result, pain elicits the stress response, producing potentially detrimental physiologic effects such as increased sympathetic tone and vasoconstriction; this can lead to decreased oxygen delivery to tissues and compensatory increases in stroke volume and heart rate (resulting in increased cardiac output). This decreased venous blood flow can result in diminished pulmonary function, which can lead to atelectasis, hypoxemia, and ventilation-perfusion mismatch.[11]

Clinically, pain, stress, and anxiety are seen most commonly as tachypnea and panting. This may worsen respiratory distress or even mask underlying lung pathology; this can be seen in dogs with laryngeal paralysis that exacerbate their dyspnea and laryngeal swelling with the anxiety of dyspnea. Although blood oxygenation improves with oxygen supplementation, resolution of dyspnea frequently requires tranquilization (e.g., acepromazine), sedation (e.g., opioids), and/or analgesia.

34.6 THERMAL RECEPTOR CHANGES

An animal's primary method of thermoregulation is evaporative cooling from the respiratory tract through an increased respiratory rate. When body temperature is above the set-point of the hypothalamic thermoregulatory center, the animal begins to pant. The set-point of the thermoregulatory center is increased in disease (e.g., fever); as a result, cooling measures may not be stimulated with elevations in body temperature. μ-Opioids (e.g., morphine, fentanyl, meperidine, methadone, oxymorphone, hydromorphone) have a similar effect in that they may falsely decrease the thermoregulatory center's set-point, which may result in tachypnea when the body temperature is normal.[12] On the other hand, opioids may also have negative effects on the central respiratory center, resulting in respiratory depression and a decreased respiratory rate and effort. Hyperthermic patients or those treated with opioids may be tachypneic, and a thorough evaluation of the respiratory system should be conducted to ensure that underlying lung disease is not present.

34.7 PERIPHERAL NERVOUS SYSTEM DISEASE

Myasthenia gravis, botulism, polyradiculoneuritis (coonhound paralysis), and tick paralysis are all examples of neuromuscular junction diseases that can lead to hypoventilation and an abnormal respiratory pattern (see Chapters 33 and 101, Chest Wall Disease and Lower Motor Neuron Disease, respectively). Stimulation of the phrenic nerve results in contraction of the diaphragm, a subsequent increase in the thoracic cavity size, and expansion of the lungs to enable oxygen delivery to small airways and alveoli. With neuromuscular junction disease, signals from the phrenic nerve to the diaphragm are dysfunctional, resulting in hypoventilation that may lead to hypercapnia and hypoxemia. As a result, chest wall and abdominal wall muscles are recruited to assist in ventilation, causing an exaggerated respiratory pattern and increased abdominal effort. Similar clinical signs may be seen with spinal cord lesions at C1 to C5 or C6 to T2 (see Chapter 99, Spinal Cord Injury). Although increasing the inspired oxygen concentration with supplementation via mask, flow-by, or nasal cannula may mildly improve blood oxygen content, the patient will remain hypercarbic without ventilatory assistance. As a result, these patients frequently require positive-pressure ventilation until correction of the primary abnormality is achieved (see Chapter 213, Basic Mechanical Ventilation).

Drugs and medications that affect the neuromuscular junction may also result in hypoventilation. Paralytic agents (e.g., pancuronium, atracurium, vecuronium), which are nondepolarizing neuromuscular junction blockers, will cause respiratory paralysis. Pancuronium is used intraoperatively to help create muscle relaxation, particularly during orthopedic or ophthalmologic procedures. These patients must be manually or mechanically ventilated until the effect of the pancuronium is reversed or wears off (approximately 30 to 45 minutes). Reversal can be accomplished by administering an anticholinesterase agent (e.g., edrophonium, physostigmine, or neostigmine) with an anticholinergic agent (e.g., atropine or glycopyrrolate) (see Chapter 183, Neuromuscular Blockers).

34.8 CENTRAL NERVOUS SYSTEM DISEASE

As previously described, the respiratory drive originates in the medulla (brain stem). Additionally, chemoreceptors that monitor PCO_2 and pH are located centrally.[2] Finally, voluntary control of breathing occurs in the cerebral cortex. With central nervous system (CNS) disorders such as head trauma, patients may manifest abnormal respiratory patterns due to edema, bleeding, or increases in intracranial pressure affecting respiratory centers. Patients with space-occupying lesions in the CNS that affect respiratory centers may also have abnormal respiratory patterns. Because respiratory system controllers are located throughout the central nervous system (e.g., medulla, cortex, chemoreceptors in various locations), a thorough cranial and peripheral nerve examination should be completed to locate additional CNS abnormalities that may help the clinician localize the disease, formulate an appropriate diagnosis, and provide timely therapy.

34.9 METABOLIC DISEASE

Metabolic disease or electrolyte imbalances may result in nonrespiratory causes of tachypnea. Hyperadrenocorticism and hyperthyroidism can affect respiratory patterns because of altered respiratory mechanics or changes in respiratory sensor inputs. Significant alterations in calcium, potassium, or glucose concentrations may result in respiratory system muscle dysfunction (e.g., diaphragm, intercostal muscles, and accessory muscles).

Dogs with hyperadrenocorticism or those undergoing glucocorticoid therapy frequently are tachypneic at rest, which may be a result of respiratory muscle weakening, muscle wasting, and/or fat deposition within the chest wall. Additionally, hepatomegaly and abdominal fat deposition may cause increased pressure on the diaphragm, which contribute to the clinical signs.[13] These animals may also suffer from pulmonary thromboembolism secondary to a hypercoagulable state.

In cats with hyperthyroidism, increased carbon dioxide production due to an increased metabolic rate (necessitating an increase in respiratory rate and ventilation), respiratory muscle weakness from muscle wasting, or occasionally hypokalemia[13] resulting from a thyroid storm (see Chapter 72, Thyroid Storm). Cats may exhibit open-mouth breathing or have clinical signs of respiratory distress while maintaining normal oxygen levels. Underlying thyroid-induced cardiomyopathy with secondary congestive heart failure may also occur, and may result in primary respiratory disease (e.g., pulmonary edema, pleural effusion); this should be clinically distinguished from a thyroid storm or other causes of nonrespiratory look-alikes.

Severe hypokalemia (<2.0 mEq/L) may result in respiratory muscle weakness causing ineffective respiration, resulting in hypoventilation and hypoxemia. Such profound, severe hypokalemia is rarely seen in dogs and cats. Potential causes of hypokalemia include insulin administration, vomiting, chronic renal failure (cats), diabetic ketoacidosis, post-obstructive diuresis, and diuretic administration (see Chapter 55, Potassium Disorders).[14]

Hypocalcemia (or more specifically, a reduction in the biologically active form, ionized calcium) may also affect respiratory muscle function (see Chapter 56, Calcium Disorders). Conditions most commonly associated with clinically significant decreases in ionized calcium include acute or chronic renal failure, acute pancreatitis, and acute eclampsia (puerperal tetany) as seen in periparturient or nursing queens and bitches.[15]

Finally, hypoglycemia may alter respiratory muscle function and diminish proper signaling from the cortex and medulla to the respiratory system. Causes of hypoglycemia in dogs and cats include excess insulin (e.g., iatrogenic, insulinoma), severe liver disease (e.g., end-stage disease, portosystemic shunt, glycogen storage disease), insulin-like hormone–secreting tumors (e.g., hepatic carcinoma, hemangiosarcoma, leiomyoma, and leiomyosarcoma), metabolic disease (e.g., hypoadrenocorticism, growth hormone deficiency), neonatal and juvenile hypoglycemia (e.g., in toy breed puppies), sepsis, and, less commonly, pregnancy toxemia, polycythemia, and hunting dog hypoglycemia.[16]

Deficiencies in potassium, calcium, or glucose should be identified rapidly via diagnostic means such as blood gas analysis or glucometry in tachypneic patients to rule out nonrespiratory look-alikes. Appropriate, prompt therapy may lead to clinical improvement while the underlying disease process is identified and addressed.

34.10 CONCLUSION

In the emergency critical care setting, veterinarians are often presented with tachypneic, panting, or even apparently dyspneic patients. Approach to the patient with respiratory distress and compromise can be one of the most daunting tasks for a practicing veterinarian. Although there is no “cookbook” approach to the dyspneic patient, an appropriate diagnostic workup (including historical findings; clinical signs; a brief, yet focused physical examination; clinicopathologic data; pulse oximetry; chest radiography; blood gas analysis, etc.) is imperative. Although the goals of this chapter are not to discuss the approach to the dyspneic patient (see Chapter 9, Tachypnea and Hypoxemia), it is imperative that the clinician be cognizant of a rapid, plausible differential list that includes nonrespiratory look-alikes. Primary respiratory system diseases should be ruled out from nonrespiratory look-alikes, as these latter causes may mask underlying respiratory disease.

34.11 SUGGESTED FURTHER READING*

American Thoracic Society: Mechanisms, assessment, and management: a consensus statement. *Am J Respir Crit Care Med*. **159**, 1999, 321–340, *A rather lengthy review of human respiratory literature. Excellent reference section*.

SP DiBartola: Metabolic acid-base disorders. In SP DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders in small animal practice*. 2000, Saunders, St. Louis, *An extremely thorough description of the pathophysiology, diagnosis, and treatment of metabolic acid-base disorders*.

EC Feldman, RW Nelson: In *Canine and feline endocrinology and reproduction*. ed 2, 1996, Saunders, Philadelphia, *A “must have” for all small animal veterinarians. Great flow charts and figures. Thorough pathophysiology on all of the main endocrine disorders*.

AM Grooters: Fluid therapy in endocrine and metabolic disorders. In SP DiBartola (Ed.): *Fluid therapy in small animal practice*. 2000, Saunders, Philadelphia, *A very useful and practical chapter highlighting fluid choices and administration in many disorders seen frequently by emergency and critical care veterinarians*.

JE Quandt, JA Lee, LL Powell: Analgesia in critically ill patients. *Compend Contin Educ Pract Vet*. **27**, 2005, 433, *An excellent review with practical application of managing pain in the emergency and critical care settings*.

* See the CD-ROM for a complete list of references

35 Chapter 35 Cardiogenic Shock

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35.1 KEY POINTS

- Cardiogenic shock is defined as inadequate cellular metabolism secondary to cardiac dysfunction, despite adequate intravascular volume.
- Clinical signs are consistent with global hypoperfusion. The aim of treatment is based on restoring cardiac output in order to normalize tissue perfusion and cellular metabolism.
- Systolic or diastolic dysfunction or arrhythmias can result in decreased stroke volume, forward flow failure, and cardiogenic shock.
- The most common cause of systolic dysfunction is dilated cardiomyopathy.
- Systolic dysfunction secondary to mechanical failure is less common. The causes include subaortic stenosis, hypertrophic obstructive cardiomyopathy, and acute mitral regurgitation secondary to ruptured chordae tendineae.
- Diastolic dysfunction can occur secondary to cardiac tamponade, hypertrophic cardiomyopathy, or tachyarrhythmias.
- Severe bradyarrhythmias such as third-degree atrioventricular block or sick sinus syndrome can lead to a severe decrease in cardiac output and thus cardiogenic shock.
- The prognosis for most forms of cardiogenic shock is guarded. A rapid diagnosis and appropriate therapeutic intervention(s) will enhance success.

35.2 INTRODUCTION

Cardiogenic shock is defined as inadequate cellular metabolism secondary to cardiac dysfunction when there is adequate intravascular volume. It is a serious life-threatening emergency and must be recognized, diagnosed, and treated as soon as possible.

The etiology of cardiogenic shock is wide ranging and varied. Consequently diagnostic modalities, case management, and definitive therapy vary with the cause. Diagnosis is based on clinical demonstration of shock along with evidence of cardiac dysfunction. Ultimately, the aim of treatment is based on restoring cardiac output in order to normalize tissue perfusion and cellular metabolism.

35.3 PATHOPHYSIOLOGY

Shock is defined as inadequate cellular energy production. It can have multiple classifications, such as distributive, metabolic, hypoxic, or cardiogenic. Decreased tissue perfusion and subsequent inadequate metabolism and energy production at the cellular level will occur when cardiac output is reduced. This occurs most commonly as a result of inadequate intravascular volume or hypovolemic shock (classified under distributive shock). In the face of adequate intravascular volume, but reduced cardiac output from cardiac dysfunction, a patient has forward failure. When forward flow failure is sufficient to cause inadequate tissue perfusion despite an adequate intravascular volume, the patient has cardiogenic shock. Heart failure can be classified as forward or backward ventricular failure. Backward flow failure occurs secondary to elevated venous pressures, and left ventricular failure (forward flow failure) occurs secondary to reduced forward flow into the aorta and systemic circulation.

Cardiac output is a product of stroke volume and heart rate (SV × HR). A decrease in either stroke volume or heart rate can therefore lead to a reduction in cardiac output. The normal physiologic response to a decrease in stroke volume is a compensatory increase in heart rate (and systemic vascular resistance) to maintain cardiac output. This is due to a baroreceptor-mediated sympathetic stimulation to preserve blood pressure and tissue perfusion. A decrease in stroke volume that cannot be reciprocally compensated for by a further increase in heart rate will lead to reduced cardiac output and forward flow failure. Similarly, forward failure may result from a severe decrease in heart rate without a primary decrease in stroke volume. Cardiogenic shock will ensue if the forward flow failure leads to decreased tissue perfusion that does not meet cellular energy demands.

Stroke volume is determined by preload, afterload, and contractility. Cardiogenic shock can ensue from alterations in any of these. For the purpose of this chapter, the cardiac cycle will be split into systole and diastole, and compromise to either phase may result in a decreased stroke volume and cardiogenic shock.

In addition to the reflex increase in heart rate, strategies exist within the body to ensure normal tissue perfusion. In response to cardiac dysfunction–induced hypotension, neurohormonal mechanisms (e.g., renin-angiotensin-aldosterone system) increase the effective circulating volume (see Chapter 6, Hypotension). This increases preload, stroke volume, and therefore cardiac output and enables the animal to maintain a normal blood pressure. As a result, forward failure in patients with chronic cardiac conditions is rare. Most patients deteriorate secondary to the increase in preload and subsequent congestive (backward) heart failure and pulmonary edema. Examples of this include chronic valvular disease in dogs and hypertrophic cardiomyopathy in cats. Some patients may suffer from concurrent forward and backward failure (e.g., dogs with dilated cardiomyopathy).

Patients that demonstrate an acute decrease in cardiac output do not have time to compensate and, as a consequence, abruptly develop cardiogenic shock (e.g., acute pericardial effusion with cardiac tamponade). These animals commonly have signs consistent with cardiogenic shock (forward failure) but may also have evidence of right-sided backward failure (ascites).

A sustained decrease in cardiac output will eventually lead to organ dysfunction. Reduced coronary blood flow may result in arrhythmias or decreased contractility and will exacerbate existing cardiac dysfunction. Inadequate renal perfusion will lead to acute renal failure, and decreased gastrointestinal perfusion may cause hemorrhagic diarrhea.

35.4 CLINICAL SIGNS AND DIAGNOSIS

Cardiogenic shock is an extreme manifestation of forward failure and clinical signs will reflect this state. Diagnosis is based on signs consistent with shock and cardiac dysfunction. It is important to realize that there is overlap among different classes of shock and that a definitive diagnosis can sometimes be difficult to ascertain.

Clinical signs are consistent with global hypoperfusion. A patient with cardiogenic shock will have a change in mentation manifested as depression, unresponsiveness, or disorientation. Peripheral extremities will be cold and the mucous membranes pale, with a prolonged capillary refill time due to intense vasoconstriction. The patient will often be tachypneic because of concurrent congestive heart failure (CHF) (pulmonary edema) or may have a compensatory respiratory alkalosis in response to a lactic acidosis. Parenchymal or pleural space disease secondary to backward failure may result in dyspnea and cyanosis.

The heart rate should be elevated in animals with cardiogenic shock unless a primary bradycardia is the cause of the cardiogenic shock or the patient is moribund. The tachycardia will be due either to an appropriate sympathetic response to hypotension or concurrent CHF, or can be a malignant arrhythmia (ventricular or supraventricular tachycardia) that is not allowing adequate diastolic filling and is the primary cause of cardiogenic shock. Correction of the malignant tachycardia in the latter case will likely improve stroke volume and cardiac output, whereas treatment of the compensatory tachycardia is contraindicated. This distinction can sometimes be difficult, and careful evaluation of the electrocardiogram and patient's volume status is necessary.

Careful auscultation of the heart and lungs should be performed. If the heart sounds are difficult to auscult, a pericardial effusion should be considered, although the clinician should not forget other causes of quiet heart sounds, including severe hypovolemia and obesity. If the patient has congestive heart failure, inspiratory crackles secondary to pulmonary edema may be heard on auscultation of the lungs, or the lungs may be quiet ventrally as a result of pleural effusion. A murmur or gallop may also be ausculted, and although extracardiac rule-outs for a heart murmur should be considered, this may provide further evidence for cardiac disease. “Synchronous” peripheral pulse palpation and cardiac auscultation should be performed to detect pulse deficits or arrhythmias.

Renal blood flow will be reduced with cardiogenic shock and may result in azotemia, with or without oliguria or anuria. Gastrointestinal tract perfusion will also be reduced and may lead to hemorrhagic diarrhea.

Venous blood gas analysis often reveals a metabolic acidosis. Inadequate cellular oxygenation may result in anaerobic metabolism and a lactic acidosis. Prerenal or renal azotemia may also contribute to the metabolic acidosis. The patient will usually have a compensatory respiratory alkalosis. If the patient has concurrent pulmonary edema the alveolar-arteriolar gradient (A-a gradient) will likely be increased on an arterial blood gas analysis (see Chapter 208, Blood Gas and Oximetry Monitoring).

An electrocardiogram should be performed on all patients that are in shock. Animals in cardiogenic shock may have a sinus tachycardia, bradyarrhythmia (e.g., AV block), or tachyarrhythmia such as atrial fibrillation or ventricular tachycardia. It is important to remember that patients with other causes of shock (e.g., distributive or hypoxic) can also have cardiac arrhythmias.

Chest radiographs should be performed when the patient is stable enough to withstand the stress of being held and may help to rule out cardiac disease as the primary cause of shock. There may be an abnormality in the cardiac silhouette and evidence of congestive or backward heart failure. Radiographic signs of CHF include enlarged pulmonary veins, an alveolar or interstitial pattern in the perihilar region (in dogs only; infiltrates are often patchy or diffuse in felines), or pleural effusion. However, it is important to remember that many animals in shock will have incidental cardiac disease that is not contributing to their morbidity. Information derived from radiographs and the electrocardiogram will not enable the clinician to definitively diagnose cardiogenic shock; rather, it should be interpreted in conjunction with clinical findings and results of other diagnostic tests.

Echocardiographic findings will vary depending on the underlying cause of cardiogenic shock. Congenital or acquired structural abnormalities, along with changes in cardiac chamber size or myocardial thickness, may be described. Pressure gradients, blood flow, and an assessment of systolic and diastolic function can be obtained. A diagnosis of cardiogenic shock may be made if there is evidence of systolic dysfunction in the presence of adequate end diastolic volume.

Even with advanced diagnostic imaging, the diagnosis of cardiogenic shock can still be difficult. A pulmonary arterial catheter (see Chapter 50, Pulmonary Artery Catheterization) can be placed to aid in both diagnosis and monitoring. A patient with cardiogenic shock will have a decreased cardiac output with an increase in the preload parameters of central venous pressure, pulmonary arterial pressure, and pulmonary arterial occlusion (wedge) pressure. This catheter can be helpful to obtain a diagnosis, guide therapy, and monitor the response to therapy.

35.5 SYSTOLIC DYSFUNCTION

Systolic dysfunction can result from a decrease in cardiac contractility or decreased flow through the left ventricular outflow tract (mechanical failure). The latter can result from a functional obstruction (e.g., aortic stenosis or hypertrophic obstructive cardiomyopathy) or severe retrograde blood flow (e.g., chordae tendineae rupture and acute, severe mitral regurgitation).

35.5.1 Failure of Contractility

35.5.1.1 Dilated Cardiomyopathy

The most common cause of cardiogenic shock resulting from systolic dysfunction is dilated cardiomyopathy (DCM) (see Chapter 38, Canine Cardiomyopathy). This condition is most commonly seen in dogs (Doberman 147 Pinscher, Boxer, Great Dane, Labrador Retriever, American Cocker Spaniel[1]) 148 and is rarely seen in cats (except those with taurine deficiency). A progressive decrease in myocardial contractility that can occur over months to years will result in a gradual decrease in stroke volume and forward failure. Activation of the renin-angiotensin system and sympathetic nervous system will stimulate renal retention of sodium and water. The increased intravascular volume results in increased in end-diastolic volume. Eccentric hypertrophy occurs secondary to cardiac myocardial stretch. These compensatory mechanisms will maintain cardiac output until the myocardial failure becomes so severe that the cardiac chambers cannot sustain further enlargement. Any further increase in intravascular volume will result in an increased end-diastolic pressure, leading to an increase in pulmonary capillary hydrostatic pressure and cardiogenic pulmonary edema in patients with left-sided heart failure or ascites in patients with right-sided heart failure.

Diagnosis of cardiogenic shock in dogs with DCM is made based on signs consistent with shock (see Clinical Signs and Diagnosis) and cardiac dysfunction. Chest x-ray films may reveal an enlarged heart along with evidence of CHF, if present. An electrocardiogram may reveal a sinus tachycardia or arrhythmias such as atrial fibrillation or ventricular tachycardia. However, it is important to remember that patients with shock from other causes (e.g., distributive or hypoxic) can also have cardiac arrhythmias.

An echocardiogram will demonstrate an enlarged and dilated heart with poor contractility. Valuable information can be gained from a pulmonary arterial catheter (see Chapters 50 and 203, Pulmonary Artery Catheterization and Hemodynamic Monitoring, respectively). This catheter will enable the clinician to measure cardiac output, as well as measure preload parameters such as central venous pressure, pulmonary arterial pressure, and pulmonary arterial occlusion (wedge) pressure. This can help in the diagnosis, prognosis, and treatment of these patients.

The aim of treating patients with systolic dysfunction is to maximize cardiac output by increasing stroke volume. Preload parameters should be monitored closely and fluids given only if necessary, or diuretics administered if the dog has congestive heart failure (see Chapter 180, Diuretics). Positive inotropic agents such as the β_1-adrenergic receptor agonist dobutamine (see Chapter 176, Vasoactive Catecholamines), phosphodiesterase inhibitors such as amrinone, pembendan, or cardiac glycosides such as digoxin (see Chapters 38 and 189, Canine Cardiomyopathy and Digoxin, respectively) can be titrated to optimize stroke volume. Optimal positive inotropic therapy has not been determined in human or veterinary medicine, and newer agents such as the calcium-sensitizing agent levosimendan are also being investigated.[2]

35.5.1.2 Sepsis

Studies in both humans and dogs have documented a dysfunctional myocardium in sepsis. Even during the hyperdynamic phase of septic shock (see Chapter 106, Sepsis) with increased cardiac output, a decrease in ejection fraction has been documented. A reduction in ventricular compliance, biventricular dilation, and a decrease in contractile function have been shown to contribute to the decrease in ejection fraction.[3] In an experimental model of septic shock, dogs in the hyperdynamic phase (with an increased cardiac output) had decreased contractility and left ventricular dilation.[3] Myocardial dysfunction peaks within days of the onset of sepsis, and has been shown to resolve within 7 to 10 days in patients who survive.[4] Low cardiac output is rare in patients with septic shock but is often due to end-stage decompensated myocardial depression.

35.5.1.3 Endomyocarditis

Endomyocarditis is a rare condition of cats that occurs several days following a routine procedure such as neutering (see Chapter 113, Endocarditis). Cats have normal myocardial function before the anesthesia and the procedure is usually uneventful, but rapid development of cardiac dysfunction, hypotension, pulmonary edema, and interstitial pneumonia develops. Although not well described, the endocardium is hyperechoic on ultrasonography, and histopathology reveals neutrophilic inflammation and fibroplasia.[5] Supportive care is recommended and, even with positive-pressure ventilation, the prognosis is poor.

35.5.1.4 Myocardial Infarction

Myocardial infarction is the number one cause of cardiogenic shock in humans, but is rarely seen in dogs (see Chapter 41, Myocardial Infarction).

35.5.2 Mechanical Failure

Cardiogenic shock resulting from mechanical failure is rare in dogs and cats. Forward flow can be reduced by an obstruction to the left ventricular outflow tract (e.g., aortic stenosis or hypertrophic obstructive cardiomyopathy) or due to severe acute retrograde blood flow as may occur with a chordae tendineae rupture.

Dogs with mitral endocardiosis and associated regurgitant flows typically have normal to increased myocardial contractility. However, when it is associated with chordae tendineae rupture, the acute and extensive mitral regurgitation will reduce forward flow sufficiently to result in cardiogenic shock and pulmonary edema.

35.6 DIASTOLIC FAILURE

Diastolic failure is due to inadequate ventricular filling. This can result from hypovolemia, a physical restriction (cardiac tamponade), inability of the myocardium to relax (hypertrophic cardiomyopathy), or inadequate time for filling (tachycardia). Diastolic failure will result in a decreased preload, and therefore a reduced stroke volume. If the animal is unable to maintain cardiac output with an increase in heart rate, cardiogenic shock ensues.

The most common cause of a decreased preload resulting in an inadequate cardiac output is hypovolemia. This is corrected by restoration of intravascular volume and is therefore not truly cardiogenic shock (see Chapters 10 and 65, Shock and Shock Fluids and Fluid Challenge, respectively).

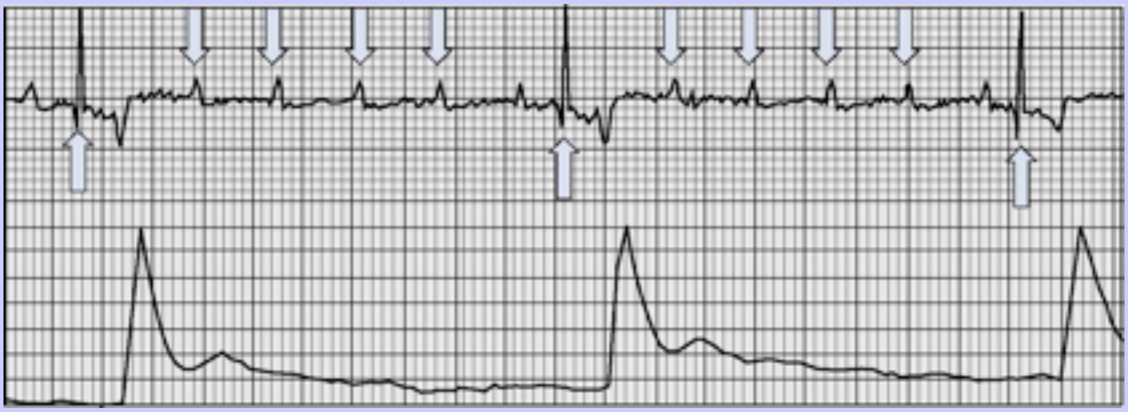
35.6.1 Cardiac Tamponade

Diastolic ventricular filling will be impaired because of the physical restriction that occurs with cardiac tamponade. Cardiac tamponade can occur secondary to pericardial effusion (see Chapters 43 and 44, Cardiac Tamponade and Pericardiocentesis and Pericardial Diseases, respectively). Effusions are most likely a result of neoplasia, but can also be secondary to a coagulopathy, trauma, atrial tear, or an idiopathic cause. The decreased diastolic ventricular filling will lead to a decrease in stroke volume and cardiac output. With the aim of maintaining normotension and tissue perfusion, a reflex tachycardia will ensue. 148 149 Eventually the increase in heart rate will not be sufficient to maintain an adequate cardiac output and the patient will become hypotensive. Cardiac auscultation will reveal quiet or absent heart sounds, leading to a high index of suspicion for a pericardial effusion; confirmation can be made quickly with ultrasonography. Despite the improved ability to visualize the heart in the presence of a pericardial effusion, a thorough echocardiogram should not be performed if a patient has cardiogenic shock. The reduced cardiac output will result in decreased tissue perfusion and a lactic acidosis. If the effusion is chronic, the patient may have decreased sodium and increased potassium concentrations from a reduced effective circulating volume-induced pseudo-hypoadrenocorticism. Because the systemic manifestations of this condition result from the decreased preload, increasing intravascular volume with a fluid bolus is warranted. However, emergency pericardiocentesis to allow for normal ventricular filling is also necessary to treat the cardiogenic shock. Pericardiocentesis in patients with coagulopathies or in dogs with a pericardial effusion secondary to an atrial tear is contraindicated, although the consequences of fulminant cardiogenic shock have to be weighed against the risk of exsanguination.

35.6.2 Hypertrophic Cardiomyopathy

Failure of normal end-diastolic volume can occur secondary to an intrinsic inability of the myocardium to relax (e.g., hypertrophic cardiomyopathy). Hypertrophic cardiomyopathy (see Chapter 37, Feline Cardiomyopathy) is the most commonly diagnosed feline cardiac disease and is characterized by concentric hypertrophy of the ventricular myocardium. Decreased end-diastolic ventricular volume due to the inability of the myocardium to relax leads to a decreased stroke volume and cardiac output. Activation of neurohormonal mechanisms will increase the intravascular volume to protect against hypotension and decreased tissue perfusion. Systolic function will normally remain adequate, and patients typically have backward (rather than forward) flow failure. However, cats with CHF that receive overzealous diuretic therapy can progress easily to hypovolemic (distributive) shock. In addition, cats with end-stage hypertrophic cardiomyopathy can also have severely impaired systolic function, leading to decreased stroke volume and cardiogenic shock. Treatment of cats with hypertrophic cardiomyopathy includes the use of β-blockers or calcium channel antagonists in an attempt to enhance lusitropy and diastolic filling (see Chapter 37, Feline Cardiomyopathy).

Figure 35-1 A lead II electrocardiogram with simultaneous arterial waveform of a patient with second-degree atrioventricular block. There are normal conducted QRS complexes *(up arrows)* with concurrent arterial pulses and nonconducted P waves *(down arrows)* with no associated cardiac output, as evidenced by an absence of an arterial pulse waveform.



35.6.3

Tachyarrhythmias

Inadequate ventricular filling occurs at elevated heart rates. End-diastolic volume is largely dependent on venous return, with atrial contraction contributing little to the normal preload. When patients become tachycardic (e.g., dogs with a heart rate over 200 beats/min), there is inadequate time for diastolic filling to occur before systole, and as a result end-diastolic volume and therefore stroke volume, are reduced. If the resultant cardiac output is compromised resulting in decreased perfusion with inadequate cellular metabolism, then the patient has cardiogenic shock. The most common cause of this malignant tachycardia is a supraventricular tachycardia (see Chapter 46, Supraventricular Tachyarrhythmias). This can be a result of primary cardiac disease or a cardiac manifestation of another systemic disease process. Therapy includes vagal maneuvers, calcium channel antagonists, and β-blockers to slow the heart rate, as well as management of the underlying condition (see Chapter 190, Antiarrhythmic Agents).

35.7

BRADYARRHYTHMIAS

Severe bradycardia can lead to such a decrease in cardiac output that cardiogenic shock ensues. The most common cause of this is severe high-grade second-degree AV block (Figure 35-1) or third-degree AV block. Animals with sick sinus syndrome can also be so severely affected that the patient can have decreased tissue perfusion and shock. In the case of third-degree AV block, AV nodal conduction does not occur and escape complexes from the bundle of His, bundle branches, or Purkinje fibers induce cardiac contraction. Extranodal heart rates are much slower than normal, with the bundle of His producing 40 to 60 beats/min, and ectopic beats from the bundle branches or distal Purkinje fibers producing 20 to 40 beats/min. Higher escape rates will be adequate for dogs at rest, but slower rates will result in a reduced cardiac output. An increase in stroke volume will occur secondary to an increased preload (due to the increased time for diastolic filling), but at low heart rates or during patient exertion, the cardiac output may be inadequate and cardiogenic shock will ensue.

Diagnosis can be made on the basis of the electrocardiographic evidence of severe second-degree or third-degree AV block or sick sinus syndrome, and other signs consistent with shock (see Clinical Signs and Diagnosis earlier in this chapter). Blood pressure may be normal, but it is important to remember that blood pressure does not equal flow. The origin of second-degree AV block can be vagally mediated or secondary to sinoatrial or AV nodal pathology. An atropine response test (0.02 to 0.04 mg/kg IV) is warranted in all cases. A β-agonist such as isoproterenol or dobutamine can be given as a constant rate infusion and will sometimes increase the heart rate sufficiently to treat the cardiogenic shock. If there is no response to medical therapy, the patient should have artificial cardiac pacing. This can be achieved by transthoracic pacing of the sedated patient, or an emergency temporary pacemaker can be placed. Intravenous fluids are contraindicated in these cases until a normal heart rate has been achieved, because preload is already increased, and a further increase in left ventricular filling pressures may result in congestive (backward) heart failure (see Chapter 45, Bradyarrhythmias and Conduction Abnormalities).

35.8 SUGGESTED FURTHER READING*

A Kumar, C Haery, JE Parrillo: Myocardial dysfunction in septic shock. Part I. Clinical manifestation of cardiovascular dysfunction. *J Cardiothorac Vasc Anesth*. **15**, 2001, 364, *An excellent review of septic shock–induced myocardial dysfunction in humans and animal models*.

MD Kittleson, RD Kienle: In *Small animal cardiovascular medicine*. 1998, Mosby, St. Louis, *A comprehensive text of small animal cardiovascular medicine. Provides in-depth information on all aspects of small animal cardiac disease*.

IH Stalis, MJ Bossbaly, TJ Van Winkle: Feline endomyocarditis and left ventricular endocardial fibrosis. *Vet Pathol*. **32**, 1995, 122, *A retrospective report describing the pathologic findings in feline endomyocarditis*.

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* See the CD-ROM for a complete list of references

36 Chapter 36 Left Ventricular Failure

Dennis E. Burkett, VMD, PhD, DACVECC

36.1 KEY POINTS

- Clinical signs of congestive left heart failure are most commonly tachypnea, dyspnea, and coughing secondary to pulmonary edema.
- Cats with congestive left heart failure commonly develop pleural effusion.
- The primary aim of managing heart failure is to prevent edema and effusion.
- Most patients with acute left heart failure are brought to the hospital in severe or fulminant left heart failure and require intensive therapy with oxygen and intravenously administered furosemide or nitroprusside, with or without dobutamine.

36.2 BASIC TERMINOLOGY

- *Circulatory failure* is present when the delivery of oxygenated blood is insufficient to meet the metabolic requirements of the body's tissues. It may result from failure of any one or more of the various components of the circulation: the heart, the vascular bed, the blood volume, or the concentration of oxygenated hemoglobin (Hgb) in the blood.[1]
- *Heart failure* is the pathophysiologic state that results when the heart is unable to pump blood at a rate that will meet the metabolic demands of the tissues and maintain normal arterial or venous pressures at rest or with exercise.[1]
- *Myocardial failure* is heart failure caused by a defect in myocardial contractility (systolic pump failure). Myocardial contractility is depressed in dogs and cats with dilated cardiomyopathy, and this is the primary functional abnormality in these patients. Not all patients with heart failure, however, have decreased myocardial contractility. For example, dogs experiencing acute rupture of a chordae tendineae suffer heart failure even though myocardial contractility is normal. Other examples include pericardial effusion, constrictive pericarditis, and acute pulmonary thromboembolism.[1]
- *Congestive heart failure* is the clinical syndrome, not a disease, wherein abnormal cardiac function results in the accumulation and retention of sodium and water with the resulting signs of congestion and edema. Most, but not all, patients with heart failure develop systemic or pulmonary congestion. Congestive signs may be absent when heart failure develops suddenly and plasma volume is normal or reduced.[1]

36.3 LEFT VENTRICULAR FAILURE

Left ventricular failure is the classic type of cardiac dysfunction that clinicians usually think of when they think of heart failure. It can occur with or without signs of heart failure. Dogs with dilated cardiomyopathy apparently have left ventricular failure for years before showing clinical evidence of heart failure.[2] Experimental cats live for years with taurine deficiency and mild to moderate left ventricular failure without signs of heart failure.[3] 151

Left ventricular failure without heart failure can be detected by echocardiography and is seen as an increase in end-systolic left ventricular diameter and decreased excursions of the left ventricular free wall and interventricular septum from diastole to systole (decreased wall motion). Left ventricular failure is always severe in dogs and cats with dilated cardiomyopathy when clinical signs become obvious. Left ventricular failure can occur secondary to other chronic diseases that affect the left ventricle, such as aortic regurgitation and patent ductus arteriosus.[4]

36.4 OTHER CAUSES OF LEFT VENTRICULAR FAILURE

Left ventricular failure frequently is absent in other left ventricular diseases, although the patient has clinical signs of heart failure. Feline hypertrophic cardiomyopathy is the classic example in veterinary medicine. Cats with this disease can have heart failure but apparently have normal myocardial contractility and enhanced left ventricular performance because of an increase in myocardial mass. Signs of heart failure occur in this disease because the heart muscle is extremely thick and therefore stiff, causing an increase in the left ventricular diastolic pressure.

Mitral regurgitation in small dogs is another example of a disease in which left ventricular failure is not the prevalent problem.[5] In this disease the major factor leading to the signs of heart failure is massive regurgitation, or leakage, of blood into the left atrium rather than a decrease in myocardial contractility.

Patent ductus arteriosus does not result in clinically significant left ventricular failure in very young dogs but can cause signs of heart failure. Left ventricular failure develops if the lesion is left untreated for months to years.[4]

Signs of heart failure are divided into those referable to congestion and edema (congestive, or backward, heart failure), to inadequate blood flow (low-output, or forward, heart failure), or to markedly decreased blood flow and low blood pressure (cardiogenic shock).[6,7] Cardiogenic shock is rare in patients with chronic heart failure, although it can occur in those that are treated vigorously with diuretics and that stop eating and drinking and become markedly dehydrated. It is identified more commonly in patients with acute heart failure[4] (see Chapter 35, Cardiogenic Shock).

36.5 RIGHT-SIDED VERSUS LEFT-SIDED HEART FAILURE

In animals with heart failure, congestion develops as a consequence of excessive venous pressure caused by the combined effects of increased plasma volume (sodium and water retention) and decreased venous capacitance (venoconstriction). With impairment of the left side of the heart, pulmonary venous pressure increases, resulting in pulmonary edema (pulmonary capillary wedge pressure >25 mm Hg) and signs of respiratory distress (left-sided CHF). Conversely, with impairment of the right side of the heart, systemic venous pressures rise, resulting in hepatomegaly and ascites (central venous pressure >15 mm Hg, right-sided CHF).

Because the capacitance of the splanchnic veins and the systemic venous reservoir is large, a rather substantial increase in blood volume is required to raise pressures in this reservoir. As a result, right-sided congestive signs tend to develop slowly. By comparison, the capacitance of the pulmonary veins is small. Relatively small changes in blood volume or its distribution can cause a rapid rise in pulmonary venous pressure and resultant pulmonary edema. Sudden increase in sympathetic tone (with fear, anxiety, or exercise) constricts the splanchnic veins, causing a shift in the circulating blood volume from the systemic to the pulmonary venous reservoir. This is one reason for the often rapid onset of pulmonary edema in animals with left-sided heart failure.[1]

36.6 CONGESTIVE LEFT-SIDED HEART FAILURE

Congestion and edema in heart failure occur because of an increase in capillary hydrostatic pressure.[6] In left-sided heart failure, increased diastolic pressure in the left ventricle (and consequently an increase in diastolic left atrial pressure, because the left ventricle and the left atrium are essentially one chamber during diastole when the mitral valve is open) or high systolic and diastolic pressures in the left atrium and pulmonary veins result in increased pulmonary capillary hydrostatic pressure, leading to pulmonary edema. Increased left ventricular diastolic pressure generally is caused either by a marked increase in blood volume and venous return to the left heart that overwhelms the ability of the heart to distend or by a stiff left ventricle that cannot accept a normal venous return at a normal pressure, or by both. Clinical signs of congestive left-sided heart failure are tachypnea, orthopnea, dyspnea, and coughing, usually secondary to pulmonary edema[4] (see Chapter 21, Pulmonary Edema).

Poor cardiac output (blood flow into the aorta per unit time) results in poor tissue perfusion and can be caused by a myriad of abnormalities that affect the ability of the left ventricle to pump properly. Poor tissue perfusion caused by a decreased cardiac output causes clinical signs of fatigue, weakness, poor exercise tolerance, cold extremities, slow capillary refill time, poor mucous membrane color, and hypothermia.[6] All of the signs except exercise intolerance will not become evident until heart failure becomes severe.

Laboratory evidence of left ventricular failure consists of a decreased cardiac output, a widened arteriovenous oxygen difference (arterial-venous oxygen content), a decreased venous oxygen tension in a patient that is not hypoxemic or anemic, and azotemia and lactic acidosis if the cardiac output is severely depressed.[7] Decreased cardiac output results in decreased tissue oxygen delivery (tissue oxygen delivery = arterial oxygen content × cardiac output). Arterial oxygen content (ml O_2/100 ml blood) is determined by the following relationship:

$$[\text{Hgb}](\text{g}/100\ \text{ml blood}) \times \text{O}_2\ \text{saturation}(\%) \times 1.34(\text{ml O}_2/\text{g Hgb})$$

The calculated value indicates the number of milliliters of oxygen carried in a given quantity of blood.

If resting tissue oxygen consumption remains stable, the actively metabolizing cells in the body must extract more oxygen from the bloodstream to meet their needs when cardiac output is reduced. This results in a decreased amount of oxygen and partial pressure of oxygen at the end of a capillary bed and on the venous side. The oxygen tension at the end of the capillary bed is the critical factor that determines oxygen delivery to the mitochondria.[8]

In animals the normal value for end-capillary or venous oxygen tension is higher than 30 mm Hg.[8] If oxygen delivery decreases enough at rest because of decreased cardiac output, it can result in the end-capillary tension or venous oxygen tension decreasing below a critical level of 20 to 24 mm Hg. When the end-capillary partial pressure of oxygen is less than 20 to 24 mm Hg, oxygen delivery to mitochondria becomes inadequate. At this stage, cells must start relying on anaerobic metabolism, resulting in lactic acid production.[7–9]

If the patient is exercising, lactic acid production in skeletal muscle results in the feeling of fatigue and forces the patient to stop. Therefore signs of left-sided heart failure are best identified in a patient that has mild or moderate heart failure either by exercising the patient and measuring blood lactate concentration or venous oxygen tension from blood draining working skeletal muscle or by obtaining a history of the patient's exercise capabilities.[10] Patients with severe heart failure may have evidence of left-sided heart failure at rest.

36.7 MODERN CONCEPT OF HEART FAILURE

36.7.1 Backward Failure Hypothesis

According to this early view of heart failure, the clinical signs result from the following sequence of events. Some cardiac insult damages the heart, leading to reduced ejection of blood. As a result, ventricular end-diastolic volume and pressure increase. As a direct consequence, atrial pressure and volume increase, leading to elevation of venous volume and pressure behind the failing ventricle(s). This, in turn, leads to increased capillary hydrostatic pressure, transudation of fluid into the interstitium, and either systemic congestion or pulmonary edema. Some refer to this hypothesis as the *backs up and leaks out* theory of heart failure.[1]

36.7.2 Forward Failure Hypothesis

This view of heart failure was formulated some 50 years after the backward failure theory. According to this hypothesis, the clinical manifestations of heart failure occur as a result of inadequate delivery of blood to the arterial system such that there is diminished perfusion of vital organs such as the brain (leading to confusion), the muscles (leading to weakness), and the kidneys (leading to sodium and water retention). As a result of reduced renal perfusion, plasma volume and extracellular fluid accumulate, leading to congestion of organs and tissues.[1]

36.7.3 Modern Concept of Heart Failure

This view of heart failure incorporates elements of both of these hypotheses, but it also offers a more comprehensive view of the importance of various cardiac and systemic compensatory responses to declining cardiac output. The current working hypothesis explaining the genesis of heart failure emphasizes that many of the systemic responses evoked by developing heart failure are identical to those evoked by hemorrhage or hypovolemia. The body responds to declining cardiac output and reduced tissue perfusion by (1) retaining sodium and water in order to increase the blood volume, (2) increasing heart rate and contractility in order to augment cardiac output, and (3) inducing generalized vasoconstriction to maintain blood pressure and ensure perfusion of vital organs such as the brain and kidney.

These compensatory responses offer some advantages to patients with developing heart failure, but eventually they result in excessive sodium and water retention (leading to congestion and edema) as well as excessive vascular resistance (resulting in mismatching of afterload to contractility and declining cardiac output). A vicious cycle is established whereby the compensatory responses evoked by heart failure cause a progressive decline in cardiac function, which leads to further activation of the same deleterious compensatory responses. To a large extent, therapeutic strategies are designed to moderate the excesses of neurohormonal activation and to reestablish a more benevolent internal milieu.[1]

36.8 MEDICAL MANAGEMENT OF CONGESTIVE LEFT-SIDED HEART FAILURE

36.8.1 Goals of Treatment

The primary goal of treatment is to achieve a cure. When this is not possible, the goals of therapy are (1) to improve the quality of life (exercise capacity and comfort at rest) and (2) to increase survival time if the quality of life is acceptable to the owner. These goals are generally accomplished by improving pump function, resolving congestion, and reducing the work of the heart.[1]

The primary aim of treating heart failure is to prevent edema and effusion. A second goal is to increase cardiac output. Almost all medical heart failure treatments are palliative rather than curative. Consequently, most patients that develop heart failure die from heart failure, often within a relatively short time. Surgical or interventional procedures are curative for select abnormalities (e.g., patent ductus arteriosus) and for a very few select patients with select abnormalities (e.g., mitral regurgitation due to myxomatous mitral valve disease).

No studies have been performed in veterinary medicine to determine if any cardiovascular drug prolongs life, although angiotensin-converting enzyme (ACE) inhibitors have been shown to prolong the time until refractory heart failure or death occurs.[4] Certainly diuretics prolong life. Without them, most patients with severe heart failure would die before leaving the hospital. Studies to prove that diuretics improve quality of life and prolong life have not been done in dogs and cats. Even in humans no large, long-term clinical trial has been performed, primarily because the Food and Drug Administration has not required such studies for regulatory approval.[11]

ACE inhibitors have been shown to prolong life in humans with heart failure. However, this prolongation is modest, usually being measured in months rather than years. Digoxin has been shown not to prolong life in humans with heart failure.[12] Often of more importance is the effect that cardiovascular drugs have on the quality of a patient's life. Diuretics and ACE inhibitors definitely improve quality of life in dogs and cats with heart failure, although diuretics are much more efficacious.[4] Pimobendan produces substantial improvement in quality of life in many dogs and may also prolong survival in those with dilated cardiomyopathy.[13,14] When heart failure 152

153 becomes refractory to these drugs, others may help reduce edema formation and improve perfusion and so reduce clinical signs and increase comfort.

In human medicine, left-sided heart failure is often staged and therapy altered depending on the stage or class. The New York Heart Association developed a classification scheme that has been used in human medicine for decades. It is based primarily on exercise limitation and ranges from class I (no exercise limitation) to class IV (inability to carry on any activity without signs). Exercise limitation is not the primary clinical abnormality that is noted by most owners of animals with left-sided heart failure. Instead, they most commonly note tachypnea, dyspnea, and coughing, or combinations of these plus respiratory difficulty resulting from pleural effusion.

Consequently, the New York Heart Association scheme is not very useful for dogs and cats. For the purposes of deciding drug therapy and dosages, we prefer to categorize our patients simply into those with mild, moderate, or severe disease and mild, moderate, severe, fulminant, or refractory left-sided heart failure (Table 36-1).[4]

Table 36-1 Suggested Drug Regimens for Treating Heart Failure Caused by the Three Most Commonly Acquired Cardiac Diseases in Dogs and Cats

Type of Heart Failure	Mitral Regurgitation: Dog	Dilated Cardiomyopathy: Dog	Hypertrophic Cardiomyopathy: Cat
Chronic mild (mild pulmonary edema, ascites, mild pleural effusion)	1. Furosemide: 1 to 2 mg/kg PO q12-48h	1. Furosemide: 1 to 2 mg/kg PO q12-48h	1. Furosemide: 3 to 6 mg/cat PO q12-48h
	2. ACEI	2. ACEI	2. Diltiazem or β-blocker
		3. Digoxin	
Chronic moderate (as above but moderate)	1. Furosemide: 1 to 2 mg/kg PO q8-12h	1. Furosemide: 1 to 2 mg/kg PO q8-12h	1. Furosemide: 6 to 12.5 mg/cat PO q12-24h
	2. ACEI	2. ACEI	2. Diltiazem or β-blocker
	3. ± Digoxin	3. Digoxin	
Chronic severe (as above but severe)	1. Furosemide: 2 to 4 mg/kg PO q8-12h	1. Furosemide: 2 to 4 mg/kg PO q8-12h	1. Furosemide: 12.5 mg/cat q8-12h
	2. ACEI	2. ACEI	2. Diltiazem and/or β-blocker
	3. ± Low-salt diet	3. Digoxin	3. ± Low-salt diet
	4. ± Digoxin	4. ± Low-salt diet	4. ± ACEI
Acute severe (severe pulmonary edema or pleural effusion)	1. Furosemide: 4 to 6 mg/kg IV q1-4h	1. Furosemide: 4 to 6 mg/kg IV q1-4h	1. Pleurocentesis
	2. Oxygen	2. Oxygen	2. Furosemide: 2 to 4 mg/kg IV or IM q2-4h
	3. ± Nitroprusside	3. ± Nitroprusside	3. Oxygen
	4. ± Hydralazine	4. ± Dobutamine	4. Do not stress
	5. ± Nitroglycerin		
Acute fulminant (massive pulmonary edema or pleural effusion with severe dyspnea)	1. Furosemide: 6 to 8 mg/kg IV q1-2h	1. Furosemide: 6 to 8 mg/kg IV q1-2h	1. Pleurocentesis
	2. Oxygen	2. Oxygen	2. Furosemide: 2 to 4 mg/kg IV or IM q1-2h
	3. ± Nitroprusside	3. ± Nitroprusside	3. Oxygen
	4. ± Hydralazine	4. ± Dobutamine	4. Do not stress
	5. ± Nitroglycerin	5. ± Nitroglycerin	

Chronic refractory (signs of heart failure despite adequate dosages of standard drugs)	1. Furosemide: 4 mg/kg PO q8h	1. Furosemide: 4 mg/kg PO q8h	1. Furosemide: 12.5 to 18.5 mg/cat q8-12h
	2. ACEI	2. ACEI	2. Diltiazem and/or β-blocker
	3. Low-salt diet	3. Low-salt diet	3. Low-salt diet
	4. ± Thiazide diuretic	4. Digoxin	4. ACEI
	5. ± Hydralazine	5. ± Thiazide diuretic	5. ± Thiazide diuretic
	6. ± A nitrate	6. ± A nitrate	6. ± A nitrate

Modified from Kittleson MD: Pathophysiology and management of heart failure. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.

ACEI, Angiotensin-converting enzyme inhibitor; *IM,* intramuscular; *IV,* intravenous; *PO,* per os.

The drugs and dosages in this table are presented as guidelines only. Drug choices must be tailored to the individual patient. *Acute:* patients that usually have been showing clinical signs for 24 hours or less and are not on current medications; *chronic:* patients showing clinical signs usually for days to weeks or patients that are being treated and now demonstrate clinical signs; ±, the drug may be used in this situation.

All patients with left-sided heart failure have severe disease. We further subdivide left-sided heart failure into acute and chronic left-sided heart failure. Most patients with this condition are brought for treatment in severe or fulminant left-sided heart failure and require intensive therapy with oxygen and intravenously administered furosemide or nitroprusside, with or without dobutamine (see Chapters 176, 178, and 180, Vasoactive Catecholamines, Antihypertensives, and Diuretics, respectively). Cats with left ventricular failure commonly develop pleural effusion, and thoracocentesis is essential to stabilize them (see Chapter 31, Thoracentesis).

Chronic left-sided heart failure is much more common than acute left-sided heart failure in veterinary medicine, 153
although patients often have signs compatible with acute decompensated left-sided heart failure. This is because 154
dogs and cats commonly hide their clinical signs or the clinical signs go unnoticed until they are severe. Chronic left-sided heart failure is graded according to the severity of the pulmonary edema on thoracic radiographs in dogs and on the severity of pulmonary edema or pleural effusion in cats.

Increasing severity of chronic left heart failure is managed with escalating dosages of furosemide, whereas an ACE inhibitor is administered at a fixed dosage. The role of pimobendan is being defined. It is approved for use in dogs with atrioventricular valvular insufficiency or dilated cardiomyopathy in the United States. Pimobendan is indicated in dogs and cats with left heart failure resulting from myocardial failure. Digoxin may also be used, depending on the underlying disease and the stage of left-sided heart failure, although it is used more frequently as an antiarrhythmic than a positive inotropic agent (see Chapter 189, Digoxin). Refractory left-sided heart failure resulting from dilated cardiomyopathy is managed by adding pimobendan, if it is not already being used, or a thiazide diuretic. The same drugs or a potent arteriolar dilator, such as hydralazine or amlodipine, may be used in dogs with refractory severe mitral regurgitation secondary to myxomatous mitral valve disease. Spironolactone is also commonly used. Although its efficacy is questionable, there is little doubt that it is safe.[4]

36.9 SUGGESTED FURTHER READING*

Consensus recommendations for the management of chronic heart failure: on behalf of the membership of the advisory council to improve outcomes nationwide in heart failure. *Am J Cardiol*. **83**, 1999, 1A, *A consensus statement from the American Heart Association regarding the value of diuretics for patients in heart failure*.

MD Kittleson: Pathophysiology and management of heart failure. In MD Kittleson, RD Kienle (Eds.): *Small animal cardiovascular medicine*. 1998, Mosby, St Louis, *Classic textbook of clinical cardiology. Excellent chapter that provides in-depth information of basic pathophysiologic mechanisms of heart failure in the context of an excellent reference textbook on cardiovascular medicine*.

RC Schlant, EH Sonnenblick: Pathophysiology of heart failure. In JW Hurst, RC Schlant, CE Rackley, et al. (Eds.): *The heart*. ed 7, 1990, McGraw-Hill, New York, *Classic textbook of human clinical cardiology. Excellent chapter that provides in-depth information about the basic pathophysiologic mechanisms of heart failure in the context of an excellent reference textbook on cardiovascular medicine*.

KT Weber, JS Janicki, CS Maskin: Pathophysiology of cardiac failure. *Am J Cardiol*. **56**, 1985, 3B, *An excellent human paper that describes the pathophysiologic cycle of heart failure. Hemodynamic features of heart failure reviewed, as well as therapeutic interventions and their mechanisms*.

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* See the CD-ROM for a complete list of references.

37 Chapter 37 Feline Cardiomyopathy

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37.1 KEY POINTS

- Myocardial disease accounts for almost all acquired cardiac disorders in the cat.
- Cardiomyopathy, defined as a heart muscle disease that is associated with cardiac dysfunction, is an important cause of both morbidity and mortality in the cat.
- The most common forms of feline cardiomyopathy result in impaired ventricular filling.
- Clinical signs are associated with congestive heart failure (CHF) or systemic thromboembolism.
- Diagnostic imaging, through radiography and echocardiography, is vital to the diagnostic approach.
- Urgent medical management of CHF secondary to feline cardiomyopathy primarily consists of supportive care and interventions that decrease ventricular filling pressures.

37.2 INTRODUCTION

Heart muscle disease is an important cause of morbidity and mortality in the cat. The various forms of myocardial disease account for virtually all acquired cardiac disorders in this species; disease that is primary to valvular structures, the pericardium, or specialized conduction system is uncommon. The nomenclature of myocardial disease is potentially problematic but evolving. Most recently, cardiomyopathy has been defined as a heart muscle disease that is associated with cardiac dysfunction.[1] Myocardial diseases generally are defined by morphopathologic features or, when it is known, cause. Based on this classification scheme, there are four basic types of cardiomyopathy: (1) dilated cardiomyopathy, (2) hypertrophic cardiomyopathy (HCM), (3) restrictive cardiomyopathy (RCM), and (4) arrhythmogenic right ventricular cardiomyopathy.[1] All of these forms are observed in the cat.[2-6]

Heart muscle diseases that are associated with a known causal agent, hemodynamic abnormality, or metabolic derangement are known as specific cardiomyopathies.[1] In the cat, the most important disorders in this category are thyrotoxic cardiomyopathy and hypertensive HCM.[7] In general, these secondary cardiomyopathies seldom result in clinical signs and are reversible when the underlying disorder resolves.[8,9]

This chapter addresses the clinical picture and therapy of cardiomyopathy that develop as a result of abnormalities that are primary to the myocardium. HCM is the most common heart disease in the cat and therefore is emphasized.

37.3 ETIOPATHOGENESIS

HCM is a primary heart muscle disease in which ventricular hypertrophy develops in the absence of a hemodynamic or metabolic cause.[10] Although systolic dysfunction and wall thinning occasionally develop in patients with long-standing HCM, the disorder generally is characterized by hypertrophy of a nondilated ventricle.[10] It is accepted that HCM in humans is a genetic disease, and this disorder has been associated with more than 200 mutations of genes that encode sarcomeric proteins. The mutation responsible for familial HCM in Maine Coon Cats has been identified.[11,12] This finding and the occurrence of HCM in related purebred and mixed breed cats, support a genetic basis.[13-15]

Feline RCM is a disorder in which impaired ventricular filling occurs in the absence of myocardial hypertrophy or pericardial disease. The structural features of RCM are varied and diagnostic criteria are not rigidly defined. The term generally is applied when there is atrial enlargement associated with a ventricle that has a normal or nearly normal appearance.[7] The cause of feline RCM is not known. Endomyocardial fibrosis and myocardial functional deficits that impair relaxation are the presumed explanations for diastolic dysfunction and resultant atrial enlargement. It is possible that some examples of RCM represent the sequelae of endomyocardial inflammation.[4]

37.4 PATHOPHYSIOLOGY

37.4.1 Diastolic Dysfunction

The ability of the ventricle to fill at low diastolic pressures depends on the rate of the active, energy-requiring process known as *myocardial relaxation,* as well as on mechanical properties that determine chamber compliance.[16] Impaired myocardial relaxation and diminished chamber compliance alter the pressure-volume relationship so that diastolic pressures are high when ventricular volume is normal or small. High diastolic pressures are reflected upstream, potentially resulting in atrial enlargement and venous congestion. In cases in which the end-diastolic volume is diminished, stroke volume may also be reduced. Therefore diastolic dysfunction can explain subnormal cardiac output as well as venous congestion.

Diastolic dysfunction is the predominant pathophysiologic mechanism responsible for clinical signs in HCM and RCM.[7] With regard to HCM, intrinsic functional deficits of the cardiomyocytes and ischemia related to hypertrophy and abnormalities of the intramural coronary arteries are responsible for impaired myocardial relaxation. Hypertrophy and fibrosis stiffen the ventricle and explain diminished chamber compliance. The basis of cardiac dysfunction in feline RCM has been defined incompletely, although endomyocardial fibrosis likely plays an important role.

Systolic anterior motion (SAM) of the mitral valve is echocardiographically detected in approximately 65% of cats with HCM.[2] The precise pathogenesis has been the subject of debate, but it is likely that abnormal drag forces are responsible for systolic movement of the valve leaflets toward the septum.[17] Abnormal papillary muscle orientation and dynamic systolic ventricular performance provide a structural and functional substrate that predisposes to SAM.[18] Movement of the mitral leaflets toward the septum results in dynamic—as opposed to fixed—left ventricular outflow tract obstruction and, usually, concurrent mitral valve regurgitation. It is relevant that SAM is a labile phenomenon. Decreases in preload and afterload or increases in contractility may provoke or augment SAM.[19] The prognostic relevance of SAM in feline HCM has not been defined. Outflow tract obstruction due to SAM has been associated with poor prognosis in humans with HCM.[20] Interestingly, the results of two retrospective studies of feline HCM suggest that SAM confers a more favorable prognosis than does its absence.[2,21] Possibly this finding reflects the limitations of retrospective evaluation of a referral population but it is nonetheless interesting. SAM is likely the most important cause of cardiac murmurs in cats with HCM.

37.5 CLINICAL PRESENTATION

37.5.1 Patient History and Physical Findings

Clinical manifestations of feline cardiomyopathy result from CHF and arterial thromboembolism (ATE). Diagnosis and management of ATE are discussed elsewhere in this volume.When CHF is present, the observation of tachypnea or respiratory distress most commonly prompts the pet owner to seek veterinary evaluation. Cats with heart failure seldom cough. Nonspecific clinical signs such as lethargy, depression, and inappetence often are observed in patients with cardiomyopathy. Although the causative disorder is usually chronic, the onset of clinical signs associated with CHF is typically sudden.

Retrospectively evaluated case series have identified an association between the administration of glucocorticoids and the development of CHF in cats.[21,22] Some affected cats may have had preexisting but clinically silent HCM, but this has not been established. This association is relevant, because the long-term prognosis for cats with glucocorticoid-associated CHF may be better than for those with CHF from more typical causes.[22]

Patients with CHF often are depressed, and hypothermia commonly is observed. The heart rates of cats with heart failure differ little from those of healthy cats,[23] although bradycardia is occasionally evident. Many cats with HCM have a systolic murmur associated with SAM. The prevalence of murmurs in cats with other forms of heart disease is lower.[5] A gallop rhythm is a subtle but important auscultatory finding. The third and fourth heart sounds are seldom audible in healthy cats. In general, auscultation of a gallop sound signifies diminished ventricular compliance in association with high atrial pressures. A gallop sound more specifically identifies cats with heart disease than does a murmur. It is important to recognize that the prevalence of murmurs in echocardiographically normal cats is not inconsequential. Because of this, the finding of a cardiac murmur is sometimes incidental to a clinical picture that results from noncardiac disease.

Crackles are sometimes heard in feline patients with cardiogenic edema, but it is likely that the auscultation of adventitious pulmonary sounds has low sensitivity and specificity for pulmonary edema. Patients in which pleural effusions are responsible for respiratory distress generally have quiet heart sounds as well as diminished, dorsally displaced bronchial tones.

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37.5.2 Electrocardiography

In the absence of arrhythmias, the diagnostic utility of electrocardiography in the assessment of cats with cardiomyopathy generally is low. Electrocardiographic evaluation of cats with clinical signs resulting from feline cardiomyopathy generally reveals sinus rhythm, although pathologic tachyarrhythmias sometimes are observed. The heart rates of cats with heart failure seldom are higher than is normal, and bradycardia resulting from a slow sinus rate or AV conduction disturbances is occasionally evident.

37.5.3 Radiography

In the cat, radiographic patterns of specific chamber enlargement are relatively indistinct. Because of this, it is seldom possible to draw conclusions regarding atrial or ventricular size, but rather, it is apparent only that the silhouette is enlarged. Radiographic cardiomegaly usually is evident when respiratory signs result from feline cardiomyopathy. Cardiogenic pulmonary edema in the cat typically is patchy but distributed diffusely through the lung (Figure 37-1). Fairly often the pulmonary arteries and veins are prominent if not obscured by infiltrates. Pulmonary edema is the most common manifestation of congestion in patients with HCM, but some cats develop large pleural effusions associated with HCM or other types of feline cardiomyopathy. Curiously, cats sometimes develop large pleural effusions as a result of cardiac diseases that affect primarily the left ventricle.

37.5.4 Echocardiography

Definitive antemortem diagnosis of feline cardiomyopathy requires echocardiographic evaluation. HCM is characterized echocardiographically by ventricular hypertrophy in the absence of chamber dilation. It is generally accepted that the end-diastolic thickness of the interventricular septum or left ventricular posterior wall is less than 6 mm in healthy cats, and measurements that exceed this figure suggest hypertrophy.[2] Left atrial enlargement resulting from diastolic dysfunction and sometimes concomitant mitral valve regurgitation is often present (Figure 37-2). This finding is clinically important, because respiratory signs rarely result from cardiomyopathy in patients with normal atrial size. It is important to know that echocardiographic pseudohypertrophy can result from hypovolemia. When this is the case, atrial dimensions typically are small.

37.5.5 Systemic Blood Pressure

Systemic blood pressure is related to both tissue perfusion and vascular resistance. Serial evaluation of blood pressure is potentially useful in the treatment of critically ill patients with feline cardiomyopathy. Because abnormal ventricular loading conditions associated with systemic hypertension may result in compensatory hypertrophy, feline HCM is a diagnosis of exclusion. Systemic blood pressure can be measured by direct puncture of a peripheral artery but more often is estimated using indirect methods. In the cat, the Doppler technique is likely to be superior to the oscillometric method.[24] Accuracy of indirect blood pressure estimation is critically dependent on technique, and results must be interpreted in context of the inherent limitations of the method and the clinical scenario. Repeatable measurements of systolic blood pressure in excess of 180 mm Hg are compatible with a diagnosis of hypertension.

37.6 DIAGNOSTIC APPROACH

The therapeutic approach to feline cardiomyopathy is best formulated based on the results of diagnostic evaluation (Figure 37-3). Clinical signs of tachypnea and respiratory distress should be investigated radiographically. When physical and radiographic findings suggest that cardiac disease is responsible, echocardiographic evaluation is indicated. When the clinical picture is complicated by arrhythmias, the patient also should be evaluated electrocardiographically. However, it is important to recognize that feline patients in respiratory distress are fragile. Sometimes the risks associated with restraint for diagnostic evaluation cannot be justified, and empiric diuretic therapy should be considered. When empirical therapy is contemplated, it is important that the presumptive diagnosis is plausible based on signalment, history, and physical findings. Furthermore, an understanding of the expected response and a willingness to adapt to changing clinical circumstances is essential.

Sometimes it is possible to perform an abbreviated echocardiographic examination while the patient is sternally recumbent, minimally restrained, and receiving supplemental oxygen. In these circumstances, it is not always important to characterize definitively the nature of the myocardial disease. Documentation of left atrial enlargement provides indirect evidence of elevated filling pressures from which it can reasonably be surmised that the clinical signs result from congestion. In most circumstances, the absence of left atrial enlargement suggests that respiratory signs are not the result of cardiac disease. It is important to note that patients who have suffered ATE often exhibit tachypnea that presumably is a manifestation of pain. In this patient population, tachypnea is inconsistently associated with congestion and it is therefore appropriate to obtain thoracic radiographs before administering diuretics to patients with ATE.

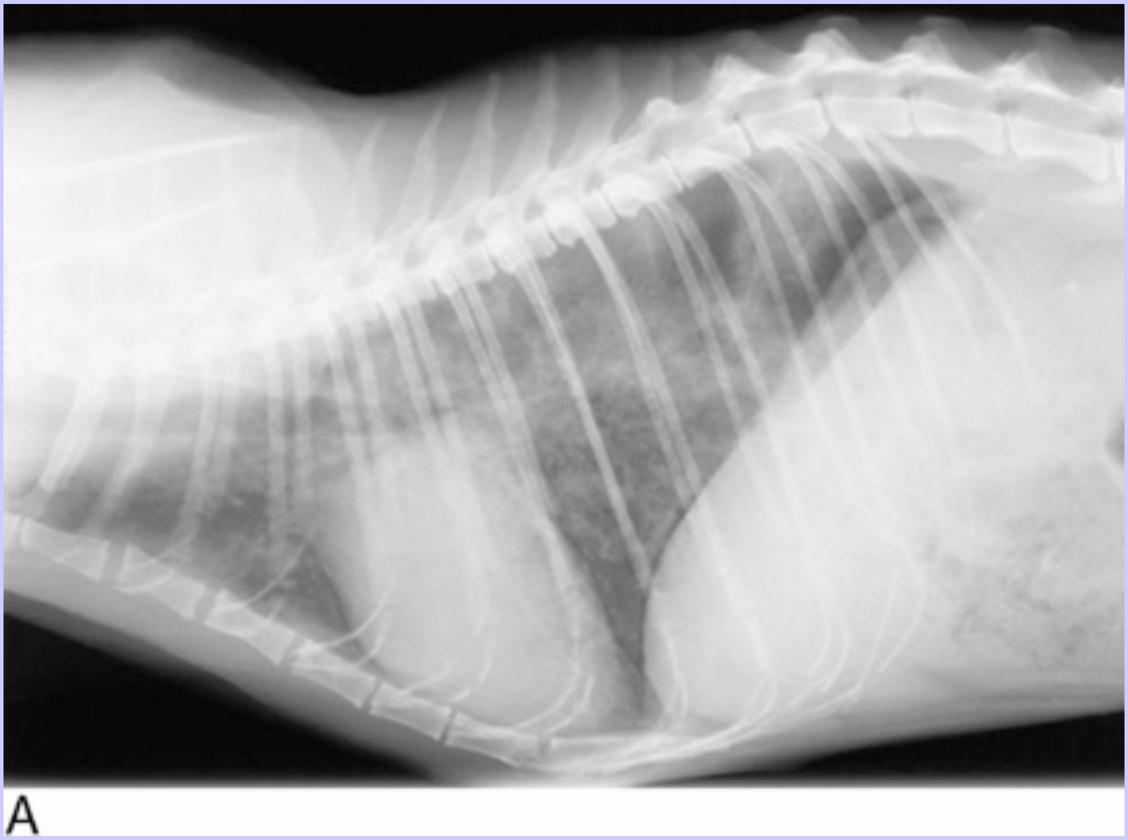
37.7 THERAPEUTIC APPROACH

37.7.1 Management of Acutely Decompensated Heart Failure

Heart failure is a syndrome that results from impaired filling or emptying of the heart. Clinical findings may reflect congestion, diminished cardiac output, or both. In veterinary patients it is necessary to use objective rather than subjective markers of disease and, therefore, feline heart failure can be defined as pulmonary edema or pleural effusion that is caused by heart disease.

General supportive measures are indicated for feline heart failure. Indirect heat sources should be used when hypothermia is present. Supplemental oxygen can be administered by mask, nasal insufflation, or via an oxygen administration cage. Most patients that respond to medical therapy for cardiogenic edema do so promptly, so mechanical ventilation generally is not required but can be considered for patients with marked respiratory distress. Pleurocentesis should be performed when physical or radiographic findings confirm that a large pleural effusion is responsible for respiratory distress. Intravenous fluids should be administered to patients with frank congestion sparingly and only if required as a vehicle for drug therapy. In animals with congestive failure, infusion of fluid further increases venous pressures but does not improve cardiac performance.

Figure 37-1 Lateral **(A)** and ventrodorsal **(B)** radiographic projections of the thorax of a cat with heart failure due to hypertrophic cardiomyopathy. The cardiac silhouette is enlarged and there are patchy interstitial and alveolar densities distributed throughout the lung.



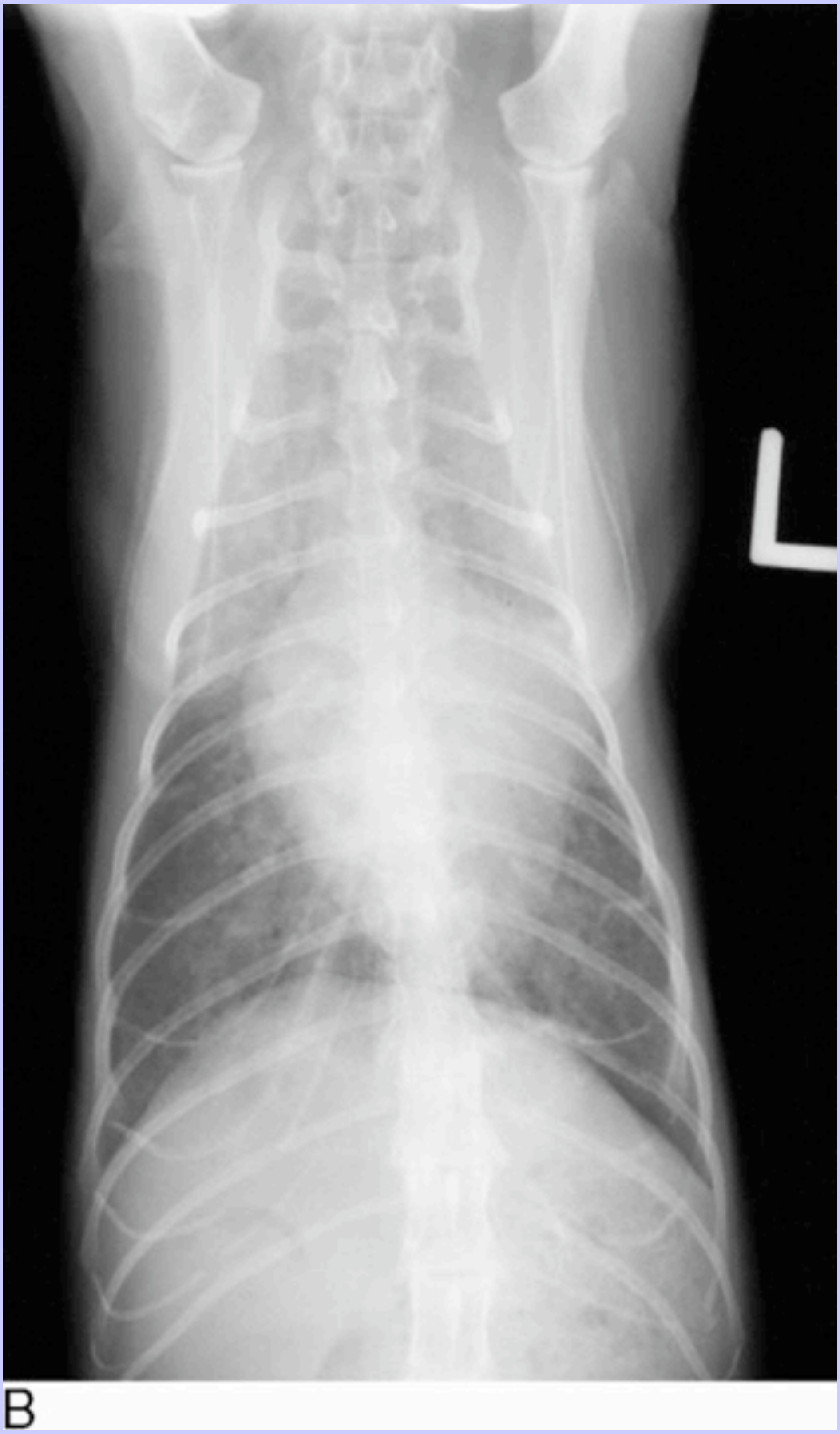

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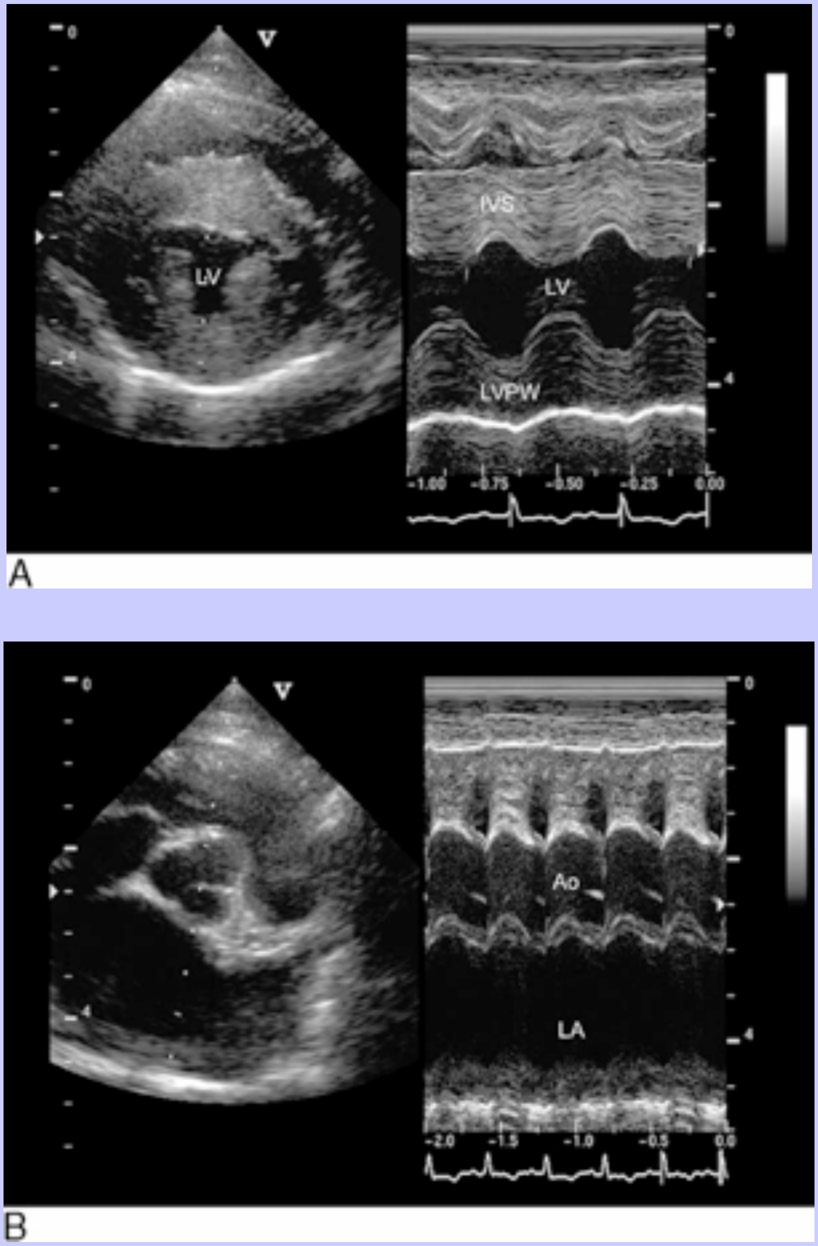
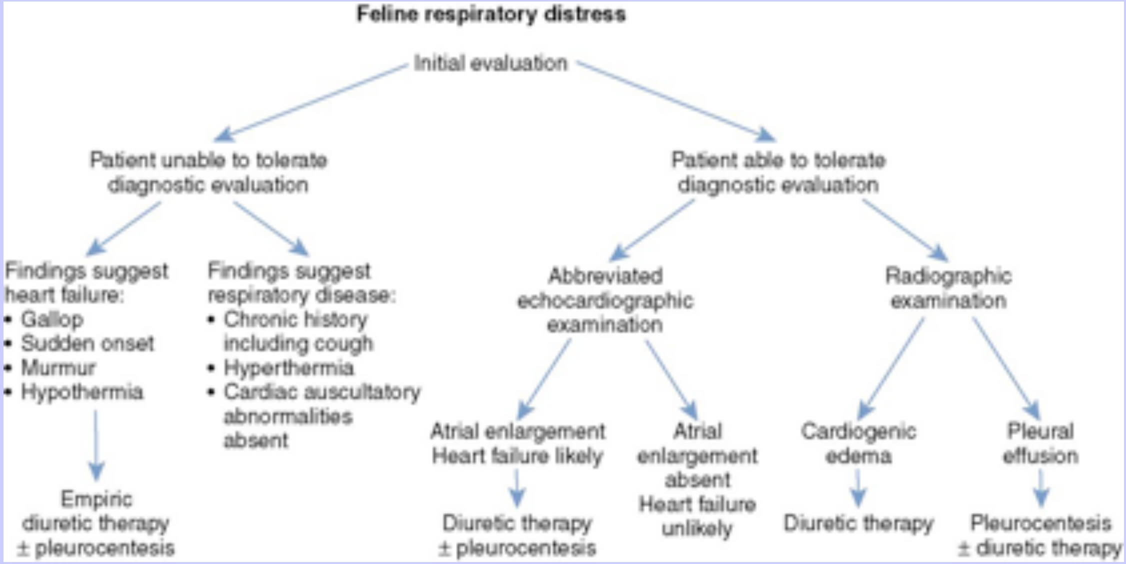
Figure 37-2 Echocardiographic images obtained from a cat with heart failure due to hypertrophic cardiomyopathy. There is moderate left ventricular hypertrophy **(A)** and left atrial enlargement **(B)**. Static two-dimensional, right parasternal short-axis images and related M-mode echocardiograms are shown for each image plane. *Ao,* Aorta; *IVS,* interventricular septum; *LA,* left atrium; *LV,* left ventricle; *LVPW,* left ventricular posterior wall.



When cardiogenic pulmonary edema is present, diuretic therapy is indicated. Furosemide is a high-ceiling loop diuretic that increases urine production and therefore reduces intravascular volume and venous pressures. Furosemide can be administered intravenously, intramuscularly, or orally. During acute decompensation, the intravenous route is preferable, but intramuscular administration is appropriate when resistance to manual restraint or other factors make intravenous administration difficult or impossible. Generally, the initial dosage is relatively high, perhaps 2 to 4 mg/kg.[25] The patient is then carefully observed for 40 to 60 minutes. If there is a decrease in respiratory rate or effort, a lower dose is administered. The dosage and interval for furosemide should be determined by clinical response. Frequent administration of low doses (0.5 to 1 mg/kg IV q1h) until respiratory signs resolve may provide a means to prevent excessive diuresis. Constant rate infusion of furosemide may accomplish the same objective, although the utility of furosemide infusion has not been specifically evaluated in the cat. If there is no change or if there is deterioration of clinical status after administration of two or three doses of parenteral furosemide, reevaluation of the presumptive diagnosis and therapeutic approach is indicated.

Figure 37-3 An algorithm that outlines one approach to the problem of feline respiratory distress; case management is determined by the tolerance of the patient and the availability of diagnostic modalities. When possible, the therapeutic approach is optimally determined by diagnostic data. It should be emphasized that these are only guidelines and that it can be difficult or impossible to distinguish cardiac and noncardiac causes of respiratory distress based only patient history and physical findings (see text for details).


Feline respiratory distress
Initial evaluation
Patient unable to tolerate diagnostic evaluation
Patient able to tolerate diagnostic evaluation
Findings suggest heart failure:
• Gallop
• Sudden onset
• Murmur
• Hypothermia
Findings suggest respiratory disease:
• Chronic history including cough
• Hyperthermia
• Cardiac auscultatory abnormalities absent
Abbreviated echocardiographic examination
Radiographic examination
Empiric diuretic therapy ± pleurocentesis
Atrial enlargement Heart failure likely
Atrial enlargement absent Heart failure unlikely
Cardiogenic edema
Pleural effusion
Diuretic therapy ± pleurocentesis
Diuretic therapy
Pleurocentesis ± diuretic therapy

It is noteworthy that the clinical profile of heart failure resulting from feline cardiomyopathy is similar to that of feline endomyocarditis.[4] The latter is an idiopathic disorder that is associated with pneumonitis. Patients typically are brought for evaluation of respiratory distress that develops soon after a stressful event, such as surgical sterilization or onychectomy. Because respiratory signs associated with this disorder are apparently not cardiogenic, diuresis is unlikely to improve clinical status.

Nitroglycerin (NG) is an organic nitrate that is sometimes used with furosemide as an adjunctive therapy that may further reduce ventricular filling pressures.[25] NG causes venodilation as well as dilation of specific arteriolar beds, including those of the coronary circulation. In veterinary medicine, NG is used principally as a venodilator that increases venous capacitance, therefore causing a decrease in ventricular filling pressures. Thus the hemodynamic effect of NG is similar to that of diuretic therapy; it is primarily a preload-reducing intervention. The efficacy of NG in feline patients has not been established. NG is most commonly administered using a transdermal cream that is applied to the pinnae or inguinal area. In humans, absorption of transdermal NG depends on the surface area of the skin to which it is applied. The dosage in feline patients is based on anecdotal evidence, but ⅛ to ¼ inch of the transdermal cream has been suggested.

Preload reduction is used for heart failure because it may effectively eliminate clinical signs of congestion. However, preload reduction generally does not improve cardiac performance. Indeed, aggressive reduction in filling pressures can decrease stroke volume, potentially resulting in hypotension. This is particularly relevant in the discussion of feline cardiomyopathy because the disorders that most commonly cause heart failure in the cats result in diastolic dysfunction. Patients with diastolic dysfunction develop congestion when ventricular volumes are normal or small. This partly explains the sensitivity of feline patients to diuretic therapy.

Patient monitoring is an important aspect of critical care. In the management of feline cardiomyopathy, the vital signs are perhaps the most important. It is useful to record body weight, body temperature, heart rate, and respiratory rate at frequent intervals. Other parameters including hematocrit, total serum protein values, blood urea nitrogen concentration, and systemic blood pressure may provide useful ancillary information.

Diastolic dysfunction resulting from HCM or RCM is the most common cause of feline heart failure. Other than furosemide, for which efficacy is assumed, no medical interventions have demonstrated efficacy for this syndrome. Based on this, the use of cardioactive ancillary therapy during acute decompensations is difficult to justify. An exception to this might be the use of antiarrhythmic agents for tachyarrhythmias that contribute to congestive signs. Primarily, the management of acutely decompensated feline cardiomyopathy consists of supportive care and judicious lowering of ventricular filling pressures.

37.7.2 Management of Chronic Heart Failure

Long-term therapy for feline myocardial disease is best guided by echocardiographic findings. Management of diastolic dysfunction traditionally has been with drugs that slow heart rate or speed myocardial relaxation or both. β-Adrenergic antagonists such as atenolol are believed to indirectly improve ventricular filling by lowering heart rate. It is likely that slowing the heart rate is beneficial when tachycardia contributes to diastolic dysfunction. Furthermore, if diastolic function is markedly impaired, myocardial relaxation may be incomplete, even when the diastolic interval and heart rate are normal. Additionally, slowing the rate may improve coronary perfusion, which presumably is abnormal in cats with HCM. Still, elevated filling pressures resulting in congestion at rest are the most obvious cause of clinical signs in HCM, and it is likely that abnormal ventricular stiffness related to hypertrophy and fibrosis is at least partly responsible. It is therefore unclear whether heart rate reduction in patients in which heart rate initially is normal can decrease venous pressures. Relevant studies are lacking and the optimal heart rate for patients with heart failure due to feline HCM is not known. β-Adrenergic antagonists may have a particular role when dynamic left ventricular outflow tract obstruction is caused by SAM and when tachyarrhythmia complicates the clinical picture.

Diltiazem is a benzothiazepine calcium channel antagonist. It is has only a modest slowing effect on heart rate but is believed to speed myocardial relaxation. The latter effect may serve to reduce ventricular filling pressures. Additionally, diltiazem may dilate coronary arteries and improve diastolic function by improving coronary perfusion. In general, diltiazem has little effect on outflow tract obstruction due to SAM.

Enalapril, an angiotensin-converting enzyme (ACE) inhibitor, also has been used in long-term management of feline HCM.[26,27] By interrupting the enzymatic conversion of angiotensin I to angiotensin II, this agent has diverse neuroendocrine effects. ACE inhibitors are vasodilators, although this effect is relatively weak. Most patients with HCM have normal or hyperdynamic systolic performance, and arteriolar dilation confers no obvious mechanical advantage. In contrast to patients with systolic dysfunction and chamber dilation, a reduction in afterload is unlikely to increase stroke volume simply because the ventricle empties almost completely in any case. Indeed, vasodilators generally are contraindicated in human HCM primarily because of the concern that vasodilation will provoke or worsen SAM.[28] The potential but theoretical benefits of ACE inhibition relate primarily to the neuroendocrine effects of these drugs. The resultant decrease in aldosterone activity might be beneficial by decreasing the renal retention of salt and water. Additionally, aldosterone and angiotensin II have been implicated as trophic factors that might be relevant to the development of hypertrophy and fibrosis.[29,30]

Unfortunately, little is known of the efficacy of ancillary therapy for feline cardiomyopathy. In a small, open-label clinical trial, the effects of diltiazem, propranolol, and verapamil on cats with pulmonary edema due to HCM were compared.[31] Diltiazem was the most efficacious of the three. However, this trial did not include a placebo group. A multicenter, randomized, placebo-controlled trial that was designed to evaluate the relative efficacy of atenolol, diltiazem, and enalapril in feline patients with CHF due to HCM or RCM has been completed.[32] The results of this study have been presented but are not yet published. The primary end point of the trial was recurrence of congestive signs, and none of the agents were superior to placebo in this regard. Patients that received enalapril remained in the trial longer than those receiving the alternatives, although this result did not achieve statistical significance. Interestingly, patients receiving atenolol fared less well than did those in the placebo group. The finding that atenolol may harm cats with pulmonary edema was possibly unexpected but is consistent with the result of the only comparable study in which propranolol administration was associated with decreased survival.[31] Studies have not addressed the effect of multivalent therapy; it is possible that β-blockers or other agents are beneficial when used in combination with furosemide and an ACE inhibitor. Regardless, based on these as yet unpublished data, the use of enalapril with furosemide seems a reasonable, initial approach to the long-term management of feline patients with CHF resulting from diastolic dysfunction.

37.8 SUGGESTED FURTHER READING*

L Ferasin, CP Sturgess, MJ Cannon, et al.: Feline idiopathic cardiomyopathy: a retrospective study of 106 cats (1994-2001). *J Feline Med Surg*. **5**, 2003, 151, *A retrospective study that provides relevant data regarding the clinical presentation of idiopathic cardiomyopathy in the cat.*

RL Hamlin: Heart rate of the cat. *J Am Anim Hosp Assoc*. **25**, 1989, 284, *A report of an observational study of heart rate in healthy cats and cats with cardiomyopathy.*

PD Pion, MD Kittleson, QR Rogers, et al.: Myocardial failure in cats associated with low plasma taurine: a reversible cardiomyopathy. *Science*. **237**, 1987, 764, *A report that documents the association of nutritional taurine deficiency and feline dilated cardiomyopathy; a landmark publication that irrevocably altered the epidemiology of feline heart disease*.

JE Rush, LM Freeman, NK Fenollosa, et al.: Population and survival characteristics of cats with hypertrophic cardiomyopathy: 260 cases (1990-1999). *J Am Vet Med Assoc*. **220**, 2002, 202, *The most recent retrospective study of feline HCM*.

* See the CD-ROM for a complete list of references.

38 Chapter 38 Canine Cardiomyopathy

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38.1 KEY POINTS

- Primary cardiomyopathies, by definition, are idiopathic diseases that are not the result of an identifiable systemic disorder or any type of congenital or acquired heart disease.
- Myocardial diseases resulting from a well-defined disease process are appropriately referred to as *secondary myocardial diseases,* and these need to be considered before the diagnosis of a primary cardiomyopathy.
- Dilated (congestive) cardiomyopathy (DCM) is the most common form of primary myocardial disease in dogs and is characterized by chamber dilation and decreased contractility.
- Large and medium sized dogs are typically affected by DCM.
- Atrial fibrillation is common and often is one of the first abnormalities detected in giant breeds with DCM such as Great Danes, Irish Wolfhounds, and Newfoundlands.
- Breed variations in canine DCM should be considered in Cocker Spaniels, Dalmatians, Boxers, Doberman Pinschers, Portuguese Water Dogs, and the giant breeds.
- Boxers with arrhythmogenic right ventricular cardiomyopathy often have syncope and, as the name states, arrhythmias (ventricular).
- Myocardial failure that leads to congestion is an emergency that requires a low-stress environment, oxygen, diuretics, vasodilators, and inotropic support.

38.2 INTRODUCTION

Primary myocardial diseases, or “true” cardiomyopathies, are those conditions that predominately affect the heart muscle, that are not the result of other congenital or acquired valvular, pericardial, vascular, or systemic diseases, and whose causes are unknown. The most common form of myocardial disease in the dog is dilated cardiomyopathy (DCM), but arrhythmogenic right ventricular cardiomyopathy (ARVC) (in Boxers) and hypertrophic cardiomyopathy (HCM) are also reported. There is increasing breed-specific information about canine DCM, especially in Doberman Pinschers, Dalmatians, Portuguese Water Dogs, Cocker Spaniels, and the giant breeds, which should be considered in diagnosis and treatment. Secondary myocardial diseases resulting from well-defined disease processes are listed in Box 38-1 and should be considered before making the diagnosis of a primary cardiomyopathy. Diagnostic and treatment techniques often are tailored to each patient and breed, with emphasis on control of a stable rhythm, prevention of congestive heart failure (CHF), and improvement in quality and length of life.

38.3 DILATED CARDIOMYOPATHY

DCM is characterized by chamber dilation and impaired systolic and often diastolic function of one or both ventricles. It is an adult-onset disease, with the exception of the Portuguese Water Dog in which the young are affected (2 to 32 weeks old). Generally, it is a disease of large and medium-sized dogs with increased incidence in the Doberman Pinscher, Great Dane, Irish Wolfhound, and American Cocker Spaniel in North American surveys, but European studies show an increased incidence in the Airedale Terrier, Newfoundland, English Cocker Spaniel, and Doberman Pinscher.[1]

38.3.1
Box 38-1 Classification of Secondary Myocardial Diseases of Dogs*

38.3.1.1
Drugs and Toxins

- Anthracyclines (doxorubicin*)
- Catecholamines
- Ionophores

38.3.1.2
Canine X-Linked Muscular Dystrophy (Duchenne)*

38.3.1.3
Infiltrative

- Glycogen storage diseases
- Mucopolysaccharidosis

38.3.1.4
Neoplastic

38.3.1.5
Ischemic

38.3.1.6
Metabolic

- Acromegaly
- Diabetes mellitus (Chapter 68, Hyperglycemic Hyperosmolar Syndrome)
- Hyperthyroidism (Chapter 73, Myxedema Coma)
- Systemic hypertension (Chapter 42, Hypertensive Crisis)

  - Idiopathic
  - Renal disease

38.3.1.7 Nutritional

L-Carnitine deficiency*

Taurine deficiency*

Vitamin E, selenium deficiency

38.3.1.8 Inflammatory

Myocarditis (Chapter 48, Myocarditis)

38.3.1.9 Infectious

Viral, bacterial, fungal, protozoal

  - Parvovirus, distemper
  - Lyme disease, trypanosomiasis

* Conditions discussed in this chapter.

38.3.2 Physical Examination

Often a soft grade 1 to 3 of 6 systolic left or right apical murmur is noted and is a result of either mitral or tricuspid valve insufficiency, respectively. Auscultation may also reveal a chaotic rhythm of atrial fibrillation or an irregular rhythm due to atrial or ventricular premature beats. With right-sided CHF the following may be noted: jugular pulses or distention or both, muffled heart and ventral lung sounds with pleural effusion (pleural fluid line), and hepatomegaly due to congestion with or without ascites. With left-sided CHF, examination will often reveal pulmonary crackles or rales, hypokinetic femoral pulses, pulse deficits with ventricular premature beats, or atrial fibrillation. Peripheral edema is rare. Finally, albeit rare, cardiogenic shock may be present as a result of decreased arterial blood pressure (usually blood pressure is normal as a result of vasoconstriction and neurohormonal activation). 160 161

38.3.3 Thoracic Radiography

Thoracic radiographs should be examined for generalized cardiomegaly and signs of CHF. Signs of left-sided heart failure include interstitial or alveolar pulmonary edema and moderate to severe left atrial enlargement.

Right-sided failure results in pleural effusion, enlarged caudal vena cava, hepatomegaly, and ascites (Figure 38-1).

38.3.4 Electrocardiography

The electrocardiogram (ECG) should be examined for sinus tachycardia, possibly with atrial or ventricular premature beats, atrial fibrillation, and ventricular tachycardia, especially in Boxers and Doberman Pinschers. Prolonged or increased voltage QRS complexes suggestive of left ventricular enlargement or low-voltage QRS complexes with pleural effusion may be noted.

38.3.5 Routine Blood Tests

Routine blood work findings are usually normal unless severe heart disease is present. Prerenal azotemia, high alanine aminotransferase levels, and electrolyte abnormalities may be evident in cases of severe heart disease. Hyponatremia and hypochloremia, if noted with CHF, are associated with a poorer prognosis. Hypokalemia, metabolic alkalosis, and prerenal azotemia may also be the result of diuretic therapy for heart disease.

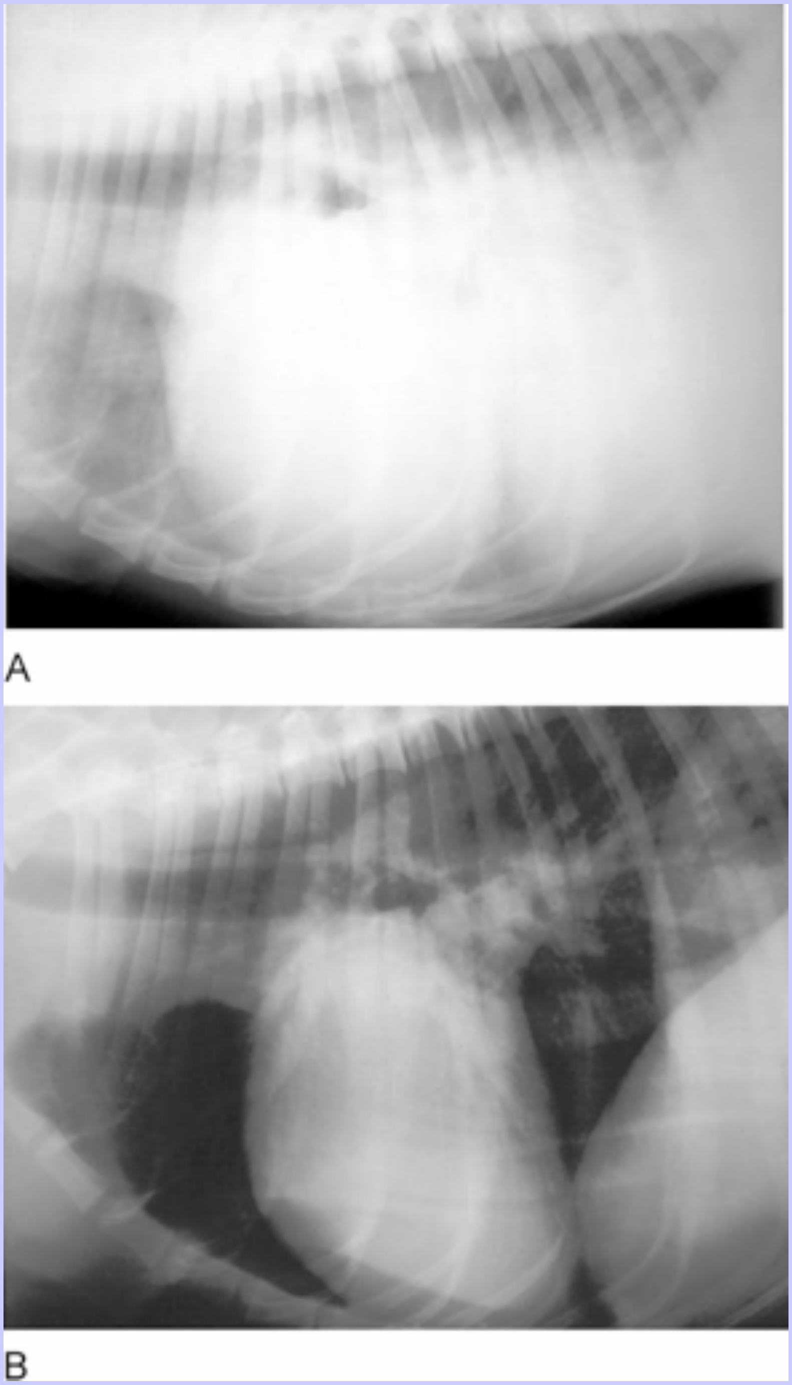
38.3.6 Effusion Analysis

Peritoneal or pleural effusion in dogs with DCM is usually a modified transudate (nucleated cell count <2500/ml, total protein <4.0 g/dl), but on occasion a chylous effusion is found.

38.3.7 Echocardiography

Ventricular and atrial dilation are common with reduced myocardial systolic function (reduced left ventricular fractional shortening percentage [FS%] and ejection fraction). Increased E-point septal separation is also common with ventricular dilation.[2] Doppler studies confirm evidence of mitral and tricuspid regurgitation, low-velocity transaortic flow, diastolic ventricular dysfunction, and possible pulmonary hypertension (due to severe left-sided heart failure). Pleural effusion can also be noted along with mild pericardial effusion due to CHF. Remember, most DCM cases with CHF should have moderate to severe atrial enlargement, and low FS% is not pathognomonic for DCM; many normal hearts contract more in apical-to-basilar direction, and this motion is not accounted for by the FS% (Figure 38-2).

Figure 38-1 Lateral radiographs of a Doberman Pinscher with dilated cardiomyopathy. **A,** On presentation. **B,** Same patient after 36 hours of aggressive treatment of congestive heart failure (furosemide, O^2, nitroprusside, dobutamine).



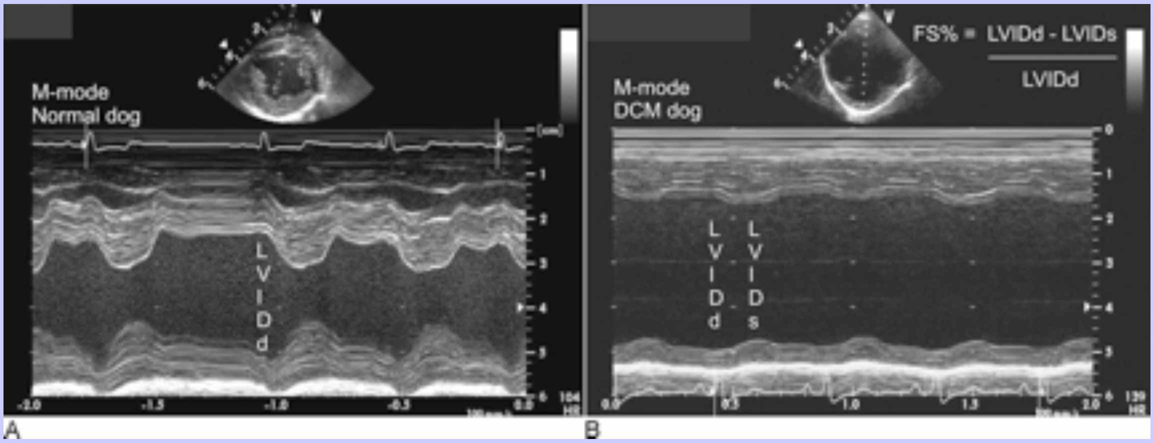
38.4 ACUTE TREATMENT OF CONGESTIVE HEART FAILURE

Acute treatment of CHF is summarized in Box 38-2. CHF failure is discussed further in Chapter 36.

38.5 LONG-TERM TREATMENT OF DILATED CARDIOMYOPATHY

Pleurocentesis and abdominocentesis should be performed as needed to relieve clinical signs.

Figure 38-2 **A,** Example of a normal dog M-mode and **(B)** an M-mode from a dog with dilated cardiomyopathy. Dog in *B* would have a decreased fractional shortening percentage based on left ventricular internal dimension in diastole – left ventricular internal dimension in systole divided by left ventricular internal dimension in diastole = LVIDd –LVIDs/LVIDd.



38.5.1 Box 38-2 Guidelines for Acute Management of Congestive Heart Failure

- Minimize stress and ensure absolute rest.
- Pleurocentesis as needed for pleural effusion (therapeutic and diagnostic).
- Oxygen supplementation.
- If pulmonary edema: Furosemide 2 to 6 mg/kg IV or IM initial dose, then 1 to 2 mg/kg q2-3h as needed for resolution of pulmonary edema, then q8-12h for the first 3 days).
- 2% Topical nitroglycerin: 1 to 2 inches q8h.
- Life-threatening arrhythmias (see Chapters 47 and 48, Ventricular Tachyarrhythmias and Myocarditis, respectively).

- Sodium nitroprusside: 2.0 μg/kg/min. If mean BP remains > 70 mm Hg increase incrementally to 4 μg/kg/min until patient is stabilized or mean pressure falls below 70 mm Hg (rate >10 μg/kg/min rarely needed); extremely effective with furosemide in managing pulmonary edema.
- Dobutamine (if severe heart failure or cardiogenic shock; ECG monitoring needed): start at 2.5 to 5 μg/kg/min, increase q3-4h by 2.5 μg/kg/min until heart rate increases excessively (>180 beats/min or >10% rise from baseline); maximum infusion rate 15 μg/kg/min. If ventricular ectopy develops, reduce rate.
- Other options for positive inotropic support include amrinone, milrinone, and pimobendan.

Note: Management should be individually tailored, based on treatment history, clinical picture, complicating arrhythmias, and concurrent diseases.

ECG, Electrocardiogram.

38.5.2 Diuretics

Diuretics are administered as needed to control edema. Furosemide is given at 1 to 4 mg/kg PO q8-24h, spironolactone at 1 to 2 mg/kg PO q12h, with or without hydrochlorothiazide 2 to 4 mg/kg PO q12h. The author often uses a combination of spironolactone-hydrochlorothiazide (Aldactazide) at 1 mg/kg PO q24h in refractory cases to decrease the number of drugs the owner has to administer (see Chapter 180, Diuretics).

38.5.3 Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors are initiated early in the therapeutic regimen, and possible drug selection includes enalapril (0.5 mg/kg PO q12-24h), benazepril (0.25 to 0.5 mg/kg PO q12-24h), and lisinopril (0.5 mg/kg PO q24h).

38.5.4 Digoxin

Digoxin is administered to improve systolic function and to slow ventricular rate in animals with supraventricular tachyarrhythmias (0.003 mg/kg PO q12h, adjusting dosage based on blood levels) (see Chapter 189, Digoxin).

38.5.5 Novel Therapy

These therapies maybe used after careful consideration of the benefits and risks involved; consultation with a cardiologist may be warranted. β-Blockers may be considered to blunt cardiotoxic effects responses of the sympathetic nervous system; however, heart failure must be well controlled and the dosage titrated slowly with careful monitoring. Carvedilol (0.5 mg/kg PO q12h; start with ¼ to ½ of a 3.125-mg tablet initially) or metoprolol (0.5 to 1 mg/kg PO q8h) can be used with caution. Pimobendan (0.25 mg/kg PO q12h) is a calcium sensitizer and a phosphodiesterase inhibitor recently approved for treatment of DCM.

38.5.6 Diet

It is important to keep patients eating an adequate level of protein, eliminate high salt–containing snacks, and in cats offer a sodium-restricted commercial diet (not at the expense of anorexia) such as Purina CV or Hills H/D.

38.5.7 Supplements

Taurine (500 mg PO q12h) is started while waiting for taurine blood levels, especially in Cocker Spaniels. Omega-3 fatty acids may improve appetite and reduce cachexia (EPA 30 to 40 mg/kg PO q24h; DHA 20 to 25 mg/kg PO q24h). Consider l-carnitine (110 mg/kg PO q12h) in American Cocker Spaniels not responding to taurine and in Boxers.

38.6 TREATMENT OF ARRHYTHMIAS

Please see Chapters 46 and 47, Supraventricular Tachyarrhythmias and Ventricular Tachyarrhythmias, respectively.

38.7 BREED VARIATIONS WITH DCM

38.7.1 Cocker Spaniels

DCM in some Cocker Spaniels is associated with low plasma taurine levels, and supplementation with taurine and l-carnitine (see earlier section for dosing) appears to improve myocardial function.[3] Normal plasma taurine levels should be over 50 ng/ml. Additional measures should be used to address complications such as arrhythmias and CHF and might be withdrawn gradually pending response to taurine (usually 3 to 4 months).

38.7.2 Doberman Pinschers

Typically considered the poster child for DCM, the Doberman Pinscher does have some unique manifestations that are important for the clinician to recognize. About 25% to 30% of Dobermans Pinschers have ventricular arrhythmias without the classic ventricular dilation seen with DCM and CHF.[4] These patients are brought in most commonly for syncope or for arrhythmias noted on routine physical examinations. Sudden death is of great concern in this breed and successful treatment of ventricular arrhythmias is imperative (see Chapter 47, Ventricular Tachyarrhythmias).

The author finds the most successful treatment consists of sotalol alone or in combination with mexiletine. A Holter monitor should be used on syncopal Dobermans Pinschers to identify the causative arrhythmia (occasionally syncope due to bradycardia in this breed)[5] and to monitor success of treatment. Dobermans Pinschers with more than 50 ventricular premature complexes (VPCs) per 24 hours, or with couplets or triplets are suspected for development of DCM. The rest of the Dobermans Pinschers have left or biventricular failure, or both, and often have atrial fibrillation. Atrial fibrillation and bilateral CHF appear to be poor prognostic signs,[6] but outlook is also affected by treatment used and client and patient compliance.

38.7.3 Dalmatians

Male dogs appear to be overrepresented in Dalmatians with DCM. All dogs in one study had left-sided heart failure with no evidence of right-sided CHF or atrial fibrillation. Dalmatians fed a low-protein diet for prevention or treatment of urate stones that develop signs consistent with DCM should be switched to a balanced protein diet.[7] Otherwise, treatment is the same as for any dog with left-sided heart failure.

38.7.4 Great Danes and Irish Wolfhounds

Atrial fibrillation is the most common finding and in some cases develops before any other evidence of underlying myocardial disease.[8] Affected dogs commonly are presented in for weight loss and loss of full exercise capacity, with occasional cough. Progression of the disease is relatively slow, especially in the Irish Wolfhounds.[8] An X-linked pattern of inheritance is suspected in some families of Great Danes, with male dogs being overrepresented.[9]

38.7.5 Portuguese Water Dogs

A juvenile form of DCM has been reported in Portuguese Water Dogs. Affected puppies die from CHF at an average age of 13 weeks after rapid disease progression.[10]

38.8 ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY IN BOXERS

In affected Boxer dogs, approximately one third have predominately left-sided failure, another one third are brought in for syncope or collapse secondary to a rhythm disturbance, and the remaining one third are asymptomatic but have rhythm disturbances (primarily ventricular arrhythmias). Atrial fibrillation occurs less frequently in Boxers than in other breeds, and cardiomegaly usually is less marked on radiographic evaluation. The pathology of Boxer dog cardiomyopathy closely resembles that seen in humans with ARVC. Similarities between the populations include etiology, clinical picture, and histopathology of fibrous fatty infiltrate of the right ventricular free wall and septum.[11] ARVC appears as an autosomal dominant trait with variable penetrance in Boxers.[12]

38.8.1 Electrocardiography

Ventricular premature beats typically have a left bundle branch block morphology in leads I, II, III, and aVF, consistent with right ventricular origin. As in the Doberman Pinschers, a Holter monitor is helpful in quantifying the VPCs and diagnosing the cause of syncope or collapse (Figure 38-3). More than 100 VPCs in a 24-hour period, periods of couplets, triplets, or runs of ventricular tachycardia may be diagnostic in a symptomatic Boxer.

38.8.2 Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy

Treatment of arrhythmias is based on clinical signs and generally is considered for animals that experience more than 500 to 1000 VPCs per 24 hours, runs of ventricular tachycardia, or evidence of R-on-T phenomenon. The author prefers sotalol (1.5 to 3 mg/kg PO q12h) with the combination of mexiletine (5 to 8 mg/kg PO q8h) in life-threatening ventricular arrhythmias in Boxers[13] (see Chapter 48, Myocarditis). Another study found that treatment with sotalol or mexiletine-atenolol was well tolerated and efficacious in Boxer dogs with ventricular arrhythmias.[14] If CHF is present, or echocardiographic ventricular and atrial dilation are noted, treatment is the same as outlined earlier for other breeds. Additionally, supplementation with L-carnitine (110 mg/kg PO q12h) might be considered, because a family of Boxers showed an improvement in systolic function with this drug.[15]

38.9 HYPERTROPHIC CARDIOMYOPATHY IN DOGS

HCM is a condition characterized by idiopathic hypertrophy of the left ventricle. The term is applied appropriately only in circumstances in which a stimulus to hypertrophy can not be identified. HCM has been recognized in only a small number of dogs and can be assumed to be an uncommon disorder.[16,17] A heritable form of hypertrophic obstructive cardiomyopathy has been described in Pointer dogs.[16] The cause of HCM in dogs is unknown. A genetic cause has been identified in most human patients,[18] but the precise pathogenic mechanism of hypertrophy remains a mystery. As with DCM, there may be more than one form (cause) of HCM.

38.9.1 Pathologic Features

The left ventricle is either symmetrically or asymmetrically hypertrophied (concentric hypertrophy), and the left atrium is dilated. Left ventricular mass is increased (heart weight–to–body weight ratio). When dynamic outflow tract obstruction is present, there is fibrosis of the anterior leaflet of the mitral valve, and a fibrous endocardial plaque on the ventricular septum opposite the mitral valve is noted. Myocardial fiber disarray, which characterizes the human form of this disease,[18] does not appear to be consistently present in affected dogs.

38.9.2 Important Differentials for Concentric Hypertrophy of the Left Ventricle

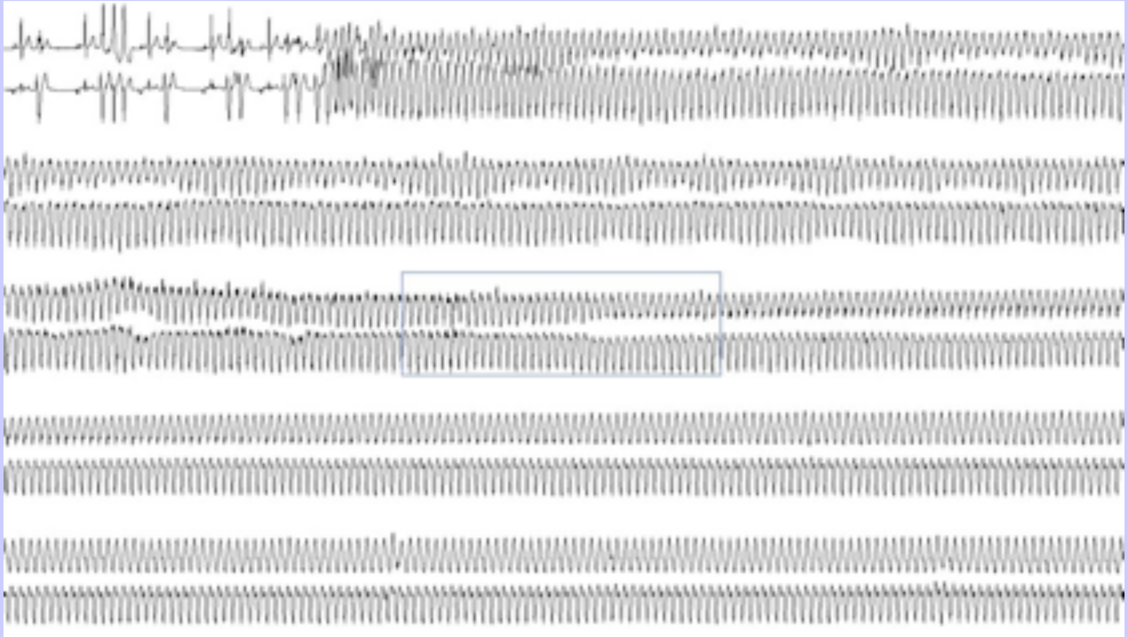
HCM and its variant hypertrophic obstructive cardiomyopathy are infrequent in dogs, and patients should be evaluated for other causes of concentric hypertrophy such as subvalvular or valvular aortic stenosis and systemic hypertension.

38.10 UNCOMMON MYOCARDIAL DISEASES OF DOGS

38.10.1 Duchenne Cardiomyopathy

Duchenne muscular dystrophy is an inherited neuromuscular disorder with an X-linked pattern of inheritance. Dystrophin, a cytoskeletal protein of the plasma membrane, is absent or defective in dogs and humans with Duchenne muscular dystrophy.[19,20] The disorder has been described best in Golden Retriever dogs.[19] Signs of skeletal muscle dysfunction predominate in most affected dogs. Some affected dogs develop deep and narrow Q waves in leads II, III, aVF, CV_6LU, and CV_6LL, and may manifest a variety of ventricular arrhythmias. Echocardiography demonstrates hyperechoic areas (fibrosis and calcification) in the left ventricular myocardium as a sequela to myocardial necrosis.[19,20] Some affected dogs develop myocardial failure resembling DCM.

Figure 38-3 Sustained ventricular tachycardia in a Boxer dog wearing a Holter monitor (24-hour recorder).



38.10.2 Atrioventricular Myopathy

Atrioventricular myopathy (silent atria, persistent atrial standstill) is a progressive idiopathic myocardial disease of dogs that may or may not be associated with a poorly characterized form of shoulder girdle skeletal muscular dystrophy. The unique features of this disorder include the marked degree of myocardial destruction and fibrosis, and the characteristic bradyarrhythmia(s) that result. Pathologic studies often reveal dilated, thin, almost transparent atria with little or no visible muscle. Involvement of the ventricles, especially the right ventricle, occurs somewhat later and is more variable. Histologic findings include variable amounts of mononuclear infiltration, myofiber necrosis and disappearance, and extensive replacement fibrosis. In dogs with muscular dystrophy, changes in skeletal muscle include muscle atrophy, hyalinized degenerated muscle fibers, and mild to moderate steatosis.[21,22] A similar cardiac disorder has been observed in human patients with Emery-Dreifuss (scapulohumeral) muscular dystrophy.

The most commonly affected dogs are English Springer Spaniels and Old English Sheepdogs. Affected dogs usually are brought in for weakness, collapse, or syncope caused by severe bradycardia. Less commonly, dogs have signs of right ventricular or biventricular CHF. Soft murmurs of atrioventricular valve insufficiency are audible in many cases. The most common ECG abnormality is persistent atrial standstill, but complete heart block and other rhythm and conduction disturbances may occur. Atrial enlargement is often found on thoracic radiographs, and generalized cardiomegaly is present in some dogs. Dilated, immobile atria can be identified by 164 echocardiography 165 or fluoroscopy. The clinical course usually is characterized by declining contractility, progressive ventricular dilation, and eventual heart failure. Management of the bradyarrhythmia by artificial pacemaker implantation usually results in immediate improvement in signs, but most dogs eventually develop refractory myocardial failure.[22]

38.10.3 Toxic Myocardial Disease

Doxorubicin (Adriamycin) and other anthracycline antibiotics can cause myocardial failure, typically after the administration of high cumulative doses (usually more than 200 to 300 mg/m^2 doxorubicin). Inasmuch as cardiac toxicity is irreversible, prevention is advised by avoiding high cumulative doses. Dexrazoxane, a cyclic derivative of ethylenediaminetetraacetic acid, protects against cardiomyopathy induced by doxorubicin and other anthracyclines, the main drawback for its use being expense.[23]

38.11 SUGGESTED FURTHER READING*

C Basso, PR Fox, KM Meurs, et al.: Arrhythmogenic right ventricular cardiomyopathy causing sudden cardiac death in Boxer dogs: a new animal model of human disease. *Circulation*. **109**, 2004, 1180, *A leading expert in human ARVC makes a case for the similarities in Boxer dogs and humans with ARVC*.

JD Bonagura, V Luis Fuentes: Echocardiography. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 5, 2000, Saunders, Philadelphia, *As always by these two authors, a nice review of echocardiography with summary of different echocardiography measurements in different breeds*.

CA Calvert, KM Meurs: CVT update: Doberman Pinscher occult cardiomyopathy. In JD Bonagura (Ed.): *Kirk's current veterinary therapy, XIII*. 2000, Saunders, Philadelphia, *A good update on occult DCM in Doberman Pinschers from a veterinarian with vast experience with this breed.*

DD Sisson, WP Thomas, BW Keene: Primary myocardial disease in the dog. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 5, 2000, Saunders, Philadelphia, *Nice summary of the prevalence of heart disease in various breeds of dogs based on the Purdue database and the author's mentor's (Sisson) vast experience. Also a great supplemental read on primary myocardial diseases in the dog*.

J Wynne: The cardiomyopathies and myocarditides. In E Braunwald (Ed.): *Heart disease*. 1992, Saunders, Philadelphia, *A great chapter with detailed information on human cardiomyopathies. Two-volume book* (Heart Disease) *read by most human and veterinary cardiologists in preparation for board examinations*.

* See the CD-ROM for a complete list of references.

39 Chapter 39 Valvular Heart Disease

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39.1 KEY POINTS

- Myxomatous valvular degeneration is the most common acquired cardiovascular disorder encountered in canine patients.
- The clinical picture of patients with valvular heart disease in the emergency setting is typically that of cardiogenic pulmonary edema (left-sided congestive heart failure).
- Virtually all patients with acquired degenerative valve disease that have congestive heart failure will have an audible cardiac murmur in the left apical position. If the patient does not have a murmur, other diagnoses should be considered.
- Radiographic and physical examination findings provide a working diagnosis for the treatment of most patients with valvular heart disease. Echocardiography is helpful but not essential for empiric emergency treatment.
- Goals of emergency therapy are to relieve symptoms of congestion, improve forward cardiac output, and improve tissue oxygenation and nutrient delivery.

39.2 INTRODUCTION

Acquired degenerative valvular disease is the most common cardiovascular disorder identified in small animals, accounting for approximately 75% of cardiovascular disease seen in dogs.[1] The condition may also be referred to as *myxomatous valvular degeneration (MVD), mitral valve prolapse, or valvular endocardiosis*. Because the mitral valve is most frequently affected, the condition is often referred to as *mitral valve disease*. This latter designation is technically incorrect, and the condition may affect all four cardiac valves.[2] For the purpose of this discussion, *myxomatous valvular degeneration* will be used to describe the condition.

MVD most frequently affects canine patients, although it may occur in any mammalian species. Feline patients rarely are affected. In the dog, small breeds are over-represented. Breeds commonly associated with the disease include the Poodle, Miniature Schnauzer, Chihuahua, Cocker Spaniel, Dachshund, Cavalier King Charles Spaniel, Lhasa Apso, Shih Tzu, and terrier breeds.[2,3] However, the differential should not be excluded in large-breed dogs with a heart murmur in the left apical position. The disease typically is seen in elderly patients, but some breeds are known to develop MVD relatively early in life (Cavalier King Charles Spaniel).[4] A male predisposition has been suggested.[7]

39.3 PATHOLOGY

The exact cellular and hormonal mechanisms that result in MVD are unknown. One attractive theory suggests that collagen degeneration and collagen synthesis are imbalanced. This is supported by the observation that chondrodystrophic breeds with other connective tissue disorders (collapsing trachea, intervertebral disk disease) frequently develop MVD.[2] Neurohormonal factors have been implicated, including serotonin and nitric oxide, but the exact role of these hormonal messengers in the development and progression of the disease is unknown.[11-13] A common misconception is that previous or chronic vegetative endocarditis from periodontal disease contributes to MVD, but evidence to support this hypothesis is lacking.

Detailed descriptions of the histologic changes that accompany MVD are beyond the scope of this discussion, and the readers are referred to other sources for this information.[3,5,6] Grossly, the changes are evident as valve thickening and elongation, which subsequently alter the normal coaptation of valve leaflets and may result in valve prolapse. The myxomatous changes have been characterized into classes of severity that are useful in a research setting, but these designations rarely are used clinically.[5]

If the degenerative changes or valve prolapse are significant, they result in a valve regurgitation that increases atrial pressure and decreases forward cardiac output (in the case of atrioventricular valve regurgitation). The degree of valvular insufficiency is dependent on the regurgitant orifice area, the pressure gradient across the valve, and the duration of systole (for the atrioventricular valves) or diastole (for the semilunar valves). In response to the decreased forward cardiac output and increased atrial pressure, several compensatory mechanisms are activated (see Pathophysiology) that result in eccentric hypertrophy (dilation) of the cardiac chambers on either side of the insufficient valve. The valve annulus then enlarges, causing further displacement of the leaflets and more regurgitation. In contrast to diseases with primary myocardial failure (i.e., dilated cardiomyopathy), ventricular function usually is maintained until late in the course of MVD, and patients frequently are symptomatic before severe myocardial failure develops. Large breed dogs may develop myocardial failure sooner during the course of the disease for reasons that are not completely understood, although increased wall stress due to a larger ventricular diameter may be a factor.[3] Many patients with MVD have a long preclinical phase before the onset of clinical signs. In these patients the murmur of valvular regurgitation frequently is identified during routine physical examination or when the patient is seen for an unrelated problem. The factors that result in progression from the asymptomatic stage to overt signs of heart failure in some dogs but not others are not completely understood.

39.4 PATHOPHYSIOLOGY

A detailed description of the pathophysiology of heart failure is presented elsewhere in this text (see Chapter 36, Left Ventricular Failure), but a brief description is presented here. Decreased forward stroke volume and decreased mean arterial pressure results in neurohormonal activation: increased sympathetic tone, activation of the renin-angiotensin-aldosterone system, and a change in the concentration of numerous other neurohormones (endothelin 1, tumor necrosis factor-α, nitric oxide).[9,10] The net result of these changes is vasoconstriction, sodium and water retention, and an increased forward cardiac output and blood pressure. This is accomplished though increased contractility (sympathetic stimulation), volume expansion, and eccentric hypertrophy. Other neurohormonal mechanisms may be activated to modulate this response (i.e., natriuretic peptide production secondary to increased atrial pressure and stretch), but these measures frequently are overwhelmed or downregulated with chronically altered cardiac output. Chronic activation of the renin-angiotensin-aldosterone system and sympathetic nervous system occurs at the expense of circulating volume and atrial pressure, which is ultimately transmitted to the pulmonary or systemic venous system. Capillary hydrostatic pressure eventually overcomes other forces in Starling's law (interstitial hydrostatic pressure and capillary oncotic pressure) that help to maintain a balance in movement of fluid across the capillary membrane, and fluid transudation results. Initially the pulmonary and systemic lymphatic systems accommodate the extra fluid transudation, but these systems eventually become overwhelmed, and overt pulmonary edema or third-space fluid accumulation result (congestive heart failure). Additional complications particular to MVD such as rupture of chordae tendineae may also occur. This may be well tolerated with a minor chord but may result in a large increase in regurgitant orifice area and left atrial pressure with acute pulmonary edema. Rarely, left atrial rupture occurs secondary to endothelial tearing at the site of impact of a high-velocity regurgitant jet. This complication results in acute tamponade (see Chapter 43, Cardiac Tamponade and Pericardiocentesis), collapse, and frequently death.

39.5 HISTORY AND PHYSICAL EXAMINATION

Patients with MVD frequently have a history of a cardiac murmur that was identified during a routine physical examination. The murmur is often chronic, although it may be a new finding in the case of chordal rupture. The intensity of the murmur has been correlated with the severity of regurgitation.[8] The patient may be brought in for evaluation of a cough, dyspnea, exercise intolerance, syncope, or collapse. Physical examination findings with left-sided heart failure are attributable to pulmonary edema: dyspnea, orthopnea, cyanosis, and abnormal lung sounds. It should be noted that all patients with pulmonary crackles do not have cardiogenic pulmonary edema, although soft crackles may be present. Tachyarrhythmias (sinus tachycardia, atrial premature contractions, or atrial fibrillation) may also be noted. Right-sided heart failure may result in the accumulation of pleural effusion or ascites, with decreased ventral lung sounds or abdominal distention, respectively. Jugular distention or pulsation should be visible in patients with right heart failure. An S_3 gallop sound may be detected with careful auscultation at the left sternal border in a patient with severe valvular disease.[8] Femoral pulses usually are strong until late in the course of the disease unless acute chordal or left atrial rupture occurs. With left atrial rupture, patients demonstrate symptoms of cardiac tamponade (see Chapter 43, Cardiac Tamponade and Pericardiocentesis).

39.6 LABORATORY EVALUATION

Laboratory findings for patients with MVD often are nonspecific. The complete blood count may be normal or may demonstrate a normochromic, normocytic nonregenerative anemia. A stress leukogram (neutrophilia, monocytosis, lymphopenia, eosinopenia) frequently is present in patients with congestive heart failure. The biochemical profile may be normal or may demonstrate abnormalities consistent with other diseases of aged patients (e.g., chronic renal failure, hepatopathies). Blood gas analysis may reveal varying degrees of hypoxemia with metabolic acidosis secondary to peripheral vasoconstriction and poor perfusion (lactic acidosis).

Research has identified several biochemical markers that may aid in the assessment of the patient with heart failure. The concentration of natriuretic peptides (ANP, BNP) is known to increase in congestive heart failure (CHF), and several studies have demonstrated that these hormones are sensitive and specific in differentiating patients with cardiogenic edema from those with dyspnea of other causes.[14] Human “bedside” analyzers for B-type natriuretic peptide are available and may eventually be included in the veterinary emergency hospital laboratory. Cardiac troponins (particularly cardiac troponin I, or cTnI) have also been investigated as blood-based biomarkers for heart disease in dogs and may be clinically applicable in the future for patients with MVD.[15,16]

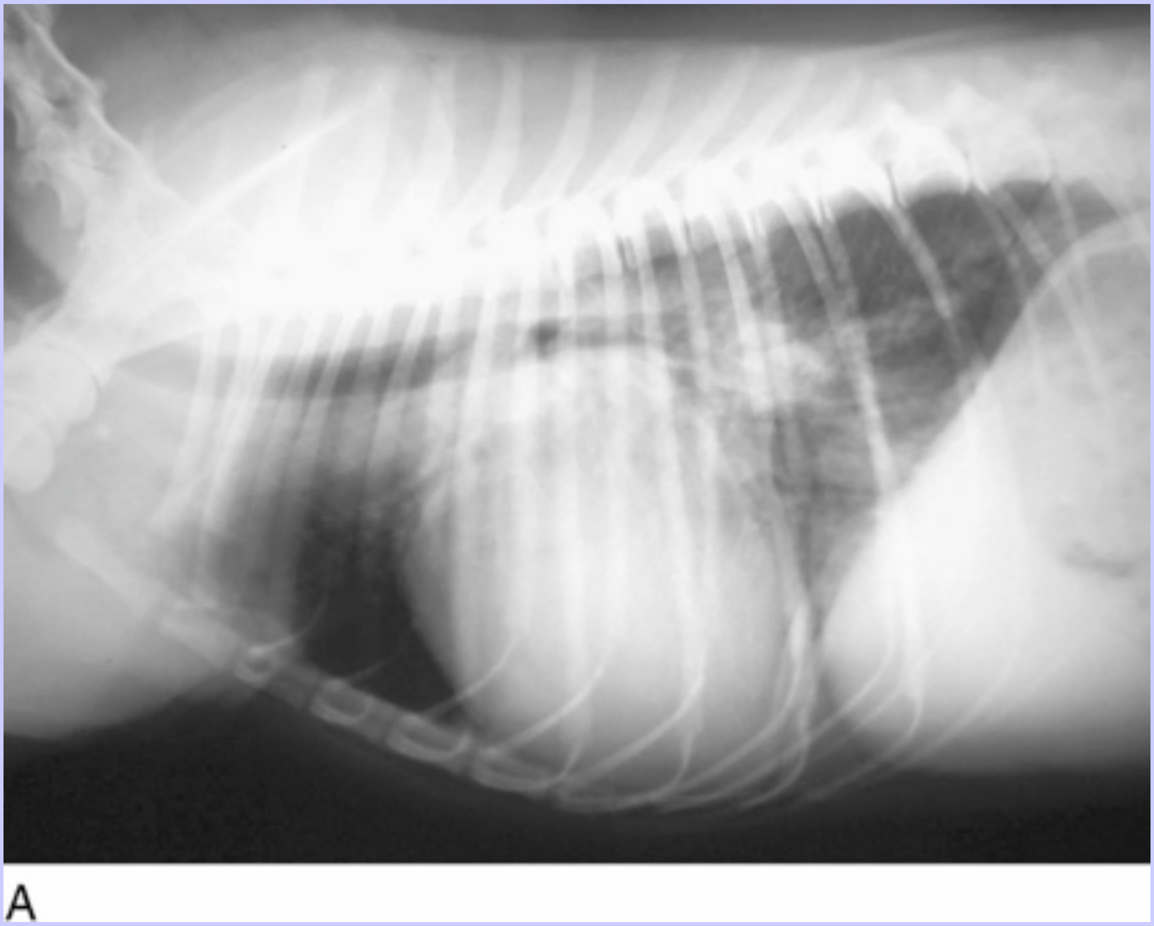
39.7 ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiogram is not a sensitive or specific diagnostic test for MVD. However, it should be performed in any patient with an arrhythmia or tachycardia. The most common rhythm changes seen in patients with MVD are sinus tachycardia, atrial premature contractions, and atrial fibrillation. Ventricular ectopy is unusual in the typical small breed dog with MVD but may occur with hypoxia, other organ system failure, or in large breeds. Other abnormalities that may be identified in canine patients include P mitrale (P wave width >40 msec), P pulmonale (P wave height >0.5 mV), or evidence of left ventricular enlargement (R wave amplitude >2.5 mV or duration >60 msec). Severe cardiac disease may be present with normal electrocardiographic findings, and the absence of these electrocardiographic changes should not be interpreted by the clinician as an indicator of normal cardiac chamber size or function.

39.8 RADIOGRAPHIC FINDINGS

The radiographic findings in canine patients with MVD and congestive heart failure CHF are illustrated in Figures 39-1 and 39-2. Left-sided heart enlargement is apparent as loss of the caudal cardiac waist (left atrial enlargement) and a tall cardiac silhouette (left ventricular enlargement). These changes result in dorsal deviation of the trachea and carina. Pulmonary venous congestion may be evident in the cranial lobar vessels on the lateral projection and the caudal lobar veins on the orthogonal projection. Dorsoventral positioning provides better visualization of the caudal pulmonary vasculature and is less stressful for the dyspneic patient than ventrodorsal positioning. Ventrodorsal positioning should be used in patients with pleural effusion for better visualization of the heart and accessory lung lobe.[17] In patients with significant tricuspid regurgitation, the heart may have changes consistent with right-sided heart enlargement (reverse “D” on dorsoventral films, increased sternal contact on lateral films). Frequently patients with advanced valvular disease will have global or generalized cardiomegaly. Pulmonary edema in the dog initially is identified as a mild, perihilar or central interstitial infiltrate. As the severity of the infiltrates increases in canine patients, they generally progress in a caudal and dorsal distribution but may be multifocal. In cases with right-sided heart failure or biventricular disease, pleural fissure lines or overt effusion may be visible and there may be a loss of serosal detail in the cranial abdomen.

Figure 39-1 Right lateral **(A)** and dorsoventral **(B)** radiographs of a dog with myxomatous valvular degeneration and severe mitral regurgitation. **A,** Severe left-sided heart enlargement is visible as an increase in overall heart size (vertebral heart score 13.0) with a tall cardiac silhouette (left ventricular enlargement) and loss of the caudal cardiac waist (left atrial enlargement). Pulmonary venous distention is visible (cranial lobar veins), and there is a hilar and caudal pulmonary interstitial pattern. The liver is enlarged. **B,** Severe generalized cardiomegaly is present with an enlarged left atrium. The pulmonary vasculature is prominent (caution must be taken in interpreting venous distention in the right caudal lobar veins because of the caudal vena cava). An interstitial pattern is visible in the caudal lung fields.



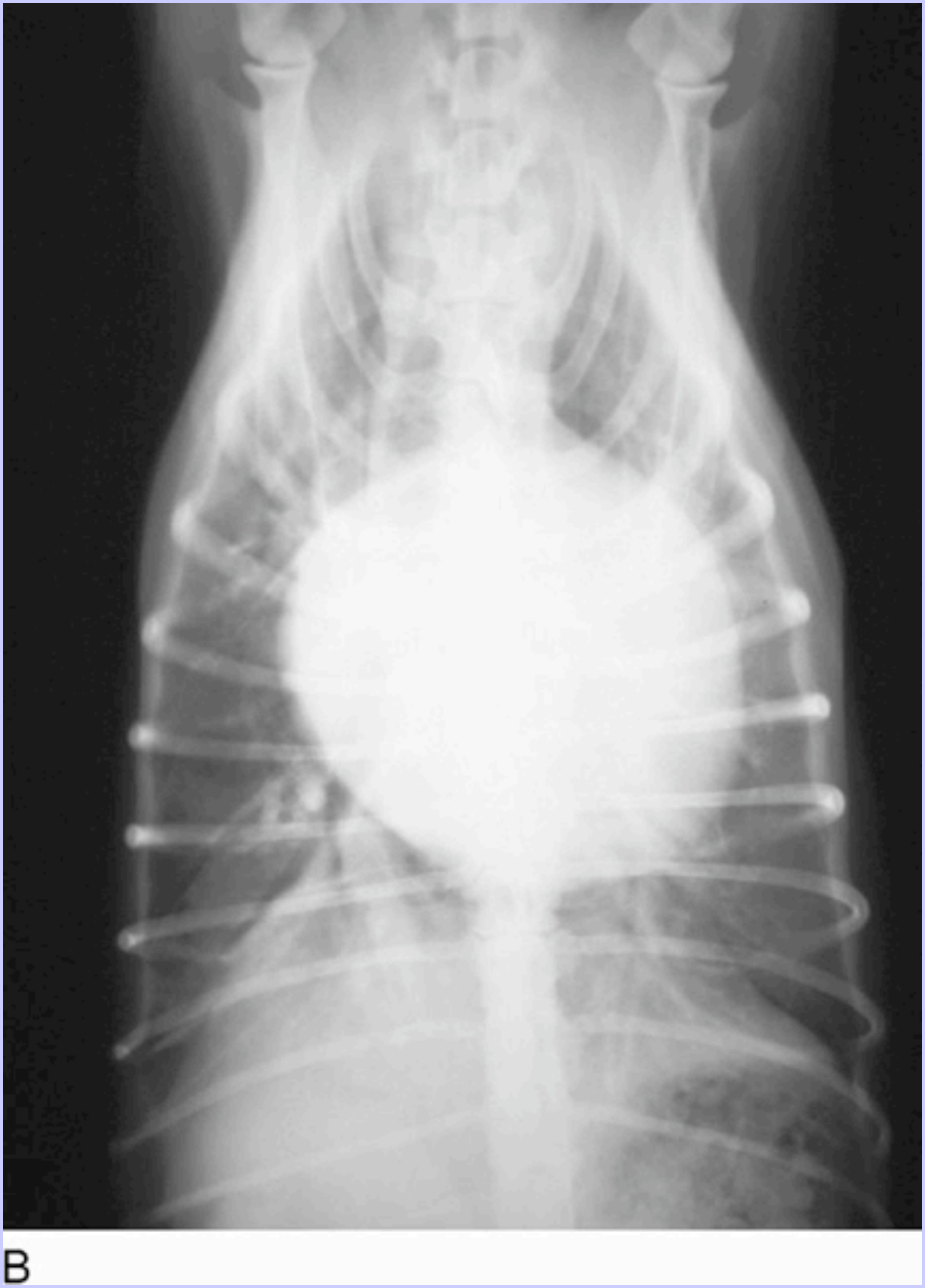
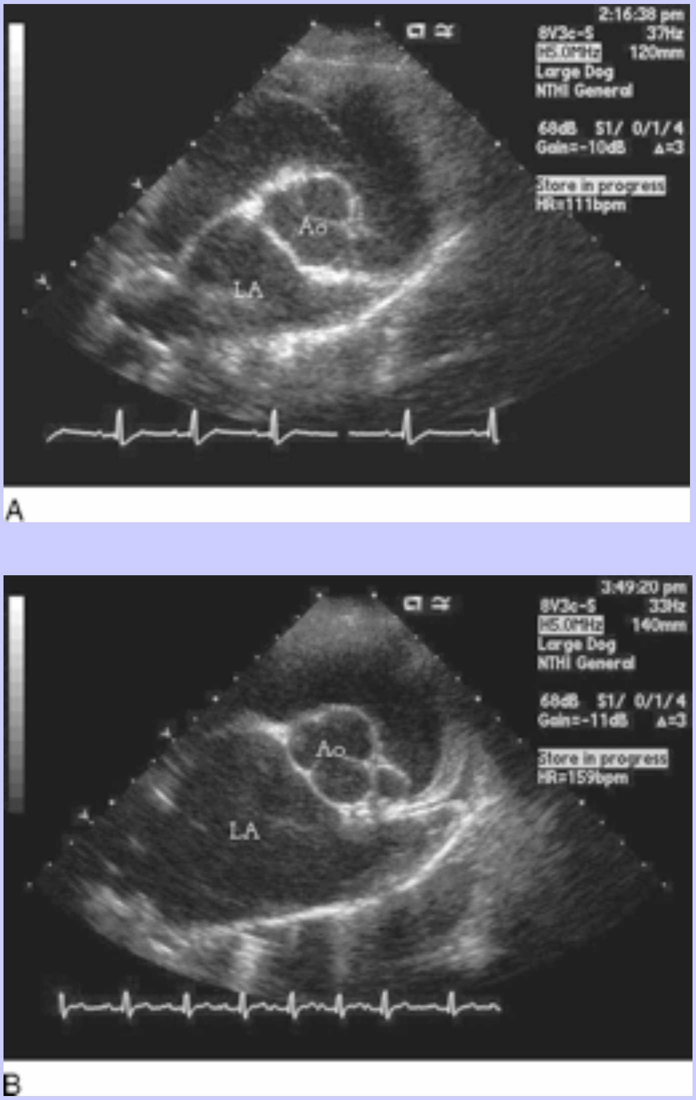

B

Figure 39-2 Right parasternal short-axis echocardiographic views of the aorta and left atrium in a normal dog **(A)** and a dog with myxomatous valve disease **(B).** The ratio of the cross-sectional dimensions of the left atrium and aorta *(LA/Ao)* should be ≤1.5 in normal dogs. In *B,* severe left atrial enlargement is present with an LA/Ao >2.0, suggestive of severe mitral regurgitation and elevated left atrial pressure. In the emergency setting, this finding may be used to support a diagnosis of congestive heart failure. The patient in *B* also has a small volume of pericardial effusion delineating the borders of the left auricle and the right ventricular outflow tract.



39.9 ECHOCARDIOGRAPHIC FINDINGS

Although echocardiography is not essential in generating an emergency medical treatment plan for patients with valvular disease, ultrasound machines are being used increasingly in the emergency setting. Echocardiography can help gauge disease severity, identify ruptured chordae tendineae, quantify pleural or pericardial effusion, confirm the diagnosis when radiographs are inconclusive, and guide therapy (i.e., thoracentesis). The classic findings in a patient with MVD affecting the mitral valve include left ventricular and left atrial dilation, hyperdynamic left ventricular wall motion, and thickened mitral valve leaflets. For the emergency veterinarian, evaluation of left atrial size is the easiest assessment and has been reviewed elsewhere.[18] In general, patients in left heart failure secondary to MVD will have a left atrium-to-aorta ratio ≥2.0 (see Figure 39-2). If this criterion is not met, other diagnoses should be considered for interstitial pulmonary infiltrates (pulmonary hypertension or thromboembolism, primary lung diseases). Other echocardiographic findings that may be identified include valve prolapse, leaflet flail (protrusion of the leaflet margin into the atrium during systole), and ruptured chordae tendineae. If available, color and spectral Doppler evaluation can confirm valve insufficiencies and offer subjective information regarding the severity of the regurgitant lesion. In patients with left atrial rupture, pericardial effusion and a pericardial thrombus may be identified. Although M-mode and spectral Doppler echocardiography offer many techniques for evaluating cardiac function in patients with MVD, these techniques are highly dependent on sonographer experience and are beyond the scope of this text. The reader is referred to other texts for descriptions of these techniques.[3,6]

39.10 EMERGENCY MANAGEMENT

As with any cause of heart failure, ideal therapy would be to reverse or correct the underlying disease. Although this is not possible in the emergency setting for a patient with MVD, several hemodynamic variables can be manipulated to improve cardiovascular function and relieve clinical signs. The goals of emergency therapy for the patient in heart failure secondary to MVD are to relieve signs of congestion, improve forward cardiac output, and improve tissue oxygenation and nutrient delivery.

39.10.1 Congestive Signs

Congestive signs can be relieved by reducing the hydrostatic pressure in the pulmonary or systemic venous system. This may be accomplished by reducing circulating volume or by venodilation. Relief of congestion usually is accomplished with diuretics to decrease intravascular volume. Furosemide is used most frequently (2 to 8 mg/kg in dogs or 1 to 4 mg/kg in cats IM or IV). A dosage-dependent venodilator effect has been observed with intravenous administration in humans.[19] A protocol for constant rate infusion of furosemide has been investigated in normal dogs and is more effective than intermittent bolus injection.[20] Other loop diuretics (bumetanide) may have greater potency but are not widely used in veterinary medicine. Oral diuretics are not ideal because of the likelihood of impaired gastrointestinal absorption and a relatively slow onset of action. In patients with refractory edema, moderate restriction of fluid intake may also be helpful in reducing congestive signs. Side effects of diuretic therapy include prerenal azotemia, electrolyte disturbances (hypokalemia, hyponatremia, others), and acid-base derangements (metabolic alkalosis). Overzealous administration of diuretics or restriction of fluids can result in uremia, dangerous reductions in circulating plasma volume, and poor tissue perfusion.

Vasodilators are not universally effective in veterinary patients, and their use should be considered adjunctive to diuretic therapy or oxygen administration. Topical nitroglycerin ointment (⅛ to ¼ inch q6h on the inner pinnae) is used most frequently. This modality increases venous capacitance in normal dogs,[21] but oral nitrates have minimal effect in normal dogs or dogs with CHF.[22]

39.10.2 Cardiac Output

Arterial vasodilators are helpful in reducing regurgitant fraction and increase forward cardiac output. Hydralazine (0.5 to 2.5 mg/kg PO q12h) has been advocated in this setting for patients with refractory heart failure.[3] Side effects of this therapy include emesis and hypotension. Amlodipine (0.2 to 0.4 mg/kg PO q12h) may also be useful and generally has fewer side effects than hydralazine. Enalapril is not a potent vasodilator in dogs and cats and generally is not recommended for emergency management of CHF. More aggressive approaches for improving forward cardiac output can be employed using an intravenous vasodilator in conjunction with a positive inotrope. This combination should be used only in settings where invasive blood pressure monitoring is available. Intravenous nitroprusside (1 to 2 μg/kg/min titrated upward to a target blood pressure) can be administered alone or in conjunction with either dopamine or dobutamine (2.5 to 10 μg/kg/min) to improve forward cardiac output and reduce capillary hydrostatic pressure. Arterial pressures should be maintained above 80 mm Hg (mean) with this regimen and can be adjusted quickly because of the short half-life of these medications. Potential complications of this therapy include severe hypotension and cyanide toxicity (with expired solutions or ≥3 days after mixing). Oral positive inotropic agents rarely are used in the emergency setting. Digoxin and other digitalis glycosides have a long half-life that limits their usefulness for acute therapy. This can be overcome with intravenous administration or oral drug loading, but these approaches may result in toxicity (see Chapters 85 and 189, Digoxin Overdose and Digoxin, respectively). Pimobendan is a new phosphodiesterase inhibitor with both positive inotropic and vasodilatory properties that has significant benefits in the management of CHF.[23,24] This drug recently has been approved for use in the United States, with a recommended oral dosage of 0.1 to 0.3 mg/kg PO q12h.

39.10.3 Tissue Oxygenation

Oxygen therapy should be considered essential for the patient in heart failure from any cause. Increasing the fraction of inspired oxygen will help improve blood oxygen content, but the impaired pulmonary function caused by edema necessitates that oxygen be used in conjunction with the therapies described above. Detailed guidelines for administration of oxygen are given elsewhere in this text (see Chapter 19, Oxygen Therapy).

39.10.4 Arrhythmia Management

Arrhythmias may be present in patients with MVD and complicate medical management. Isolated atrial or ventricular premature contractions rarely require therapy, but atrial fibrillation and ventricular or supraventricular tachycardia should be identified and addressed. These frequently result in a rapid heart rate that decreases diastolic filling and affects forward cardiac output. Tachyarrhythmias may also decrease systolic function and result in myocardial failure if they are chronic (tachycardia-induced cardiomyopathy). Pharmacologic management of these arrhythmias is discussed elsewhere in this text (see Chapters 46 and 47, Supraventricular Tachyarrhythmias and Ventricular Tachyarrhythmias, respectively). Direct current cardioversion may be employed for rhythms that are refractory to medical management (see Chapter 53, Cardioversion and Defibrillation).

39.10.5 Monitoring

Successful treatment of a patient with CHF from MVD requires monitoring of volume status, renal function, acid-base balance, and blood pressure. When patients are admitted in an emergency setting, a complete blood count, biochemical profile, urine specific gravity and thoracic radiographs should be obtained before initiation of therapy (condition permitting). Twelve to 24 hours after initiation of therapy, a blood gas analysis, biochemical profile with electrolytes, and thoracic radiographs should be repeated. If a patient develops significant azotemia (blood urea nitrogen >50 mg/dl, creatinine ≥2.5 mg/dl), dehydration, alkalosis, or electrolyte disturbances, diuretic therapy should be modified and alternative modalities employed.

39.11 LONG-TERM THERAPY

In general, the goals of long-term therapy for MVD mirror those of the emergency setting but with orally administered medications. The precise timing for initiation of therapy before the onset of CHF is a subject of much debate because clinical trials have demonstrated variable results with the early use of angiotensin-converting enzyme (ACE) inhibitors.[29,30] The initial treatment of patients with MVD and CHF should include a diuretic at the lowest effective dosage and an ACE inhibitor. A balanced low-salt diet should also play an integral role in the management of a patient's congestion and may reduce the dosage of diuretics required to control signs of edema. As heart failure progresses or complications such as atrial arrhythmias or systolic dysfunction develop, digoxin is often added to this regimen. Adjunctive therapies (potassium gluconate and cough suppressants) are used on a case-by-case basis. When patients develop edema that is refractory to this therapy, additional diuretics (spironolactone), positive inotropic agents (pimobendan where available), and vasodilators (amlodipine, hydralazine) are used in various combinations depending on the patient's coexisting disease states, ventricular function, and tolerance of therapy. For patients whose disease is refractory to medical therapy, surgical intervention is a newer therapeutic modality that is offered at selected teaching institutions.[25-27]

39.12 PROGNOSIS

In general, MVD carries a more favorable prognosis than many other cardiovascular diseases. The condition has a long (1 to 2 years) preclinical phase when patients have an excellent quality of life with few clinical signs. When CHF signs develop, the prognosis worsens. Medical therapy may offer patients the possibility of approximately 1 year of good-quality life after the onset of CHF.[28] Patients with ruptured major chordae tendineae or a ruptured left atrium have a poor or grave prognosis. When patients decompensate while receiving long-term oral medications, aggressive parenteral therapy can still offer the possibility of partial recovery and return to life at home with oral medication.

39.13 INFECTIOUS ENDOCARDITIS

This condition is presented here because of the similar hemodynamic changes that develop with valve regurgitation caused by vegetative lesions, but the condition is not typically associated with MVD. With the exception of one case report,[31] no published data are available that would suggest that MVD predisposes dogs to bacterial endocarditis. For detailed descriptions of this disease the reader is referred to other texts.[32,33]

Bacterial infection of valvular structures in the heart is a rare cause of CHF in domestic animals. In dogs and cats, the aortic and mitral valves are affected most frequently, and the tricuspid and pulmonic valves are rarely affected.

The condition is identified rarely in the cat and infrequently in the dog, and large breed males are overrepresented. The most common causative agents in the dog include *Staphylococcus* spp, *Streptococcus* spp, and *Escherichia coli,* although many more agents have been identified. *Bartonella* species are emerging as important causes of culture-negative endocarditis in dogs and humans.[34] Physical examination findings may mimic those of a patient with degenerative valve disease, but a spectrum of other clinical findings should alert the clinician to the possibility of vegetative endocarditis: fever, hemogram results consistent with sepsis, coagulopathies, lameness, and evidence of multiorgan involvement or failure (septic emboli). Secondary immune-mediated disorders (e.g., glomerulonephritis) are also common sequelae. A portal of entry for the bacteria is not often identified, and other predisposing factors (e.g., indwelling catheters) should be considered for patients with endocarditis. Patients with endocarditis frequently have acute valvular regurgitation, and the classic radiographic appearance of the heart in a patient with MVD may not necessarily be present. Echocardiography plays a more important role in the management of vegetative endocarditis than of MVD by confirming the presence of vegetative lesions, characterizing the severity of the valve damage, and offering a prognosis. Definitive diagnosis is often elusive, and criteria have been defined to help remedy this problem. Management of patients with vegetative endocarditis should include an effort to identify the causative agent (blood cultures, urine culture, and culture of open wounds or indwelling catheters), culture and sensitivity–directed intravenous antibiotic therapy, and supportive care for other organ systems that may be affected by septic embolization. If sensitivity data are not available, broad-spectrum intravenous antibiotics should be used. Frequently antibiotics are required for long periods (>6 weeks). Therapy for CHF should be identical to that described for other types of valvular heart disease discussed in this chapter and elsewhere.

39.14

SUGGESTED FURTHER READING*

MD Kittleson: Infective endocarditis (and annuloaortic ectasia). In MD Kittleson, RD Kienle (Eds.): *Small animal cardiovascular medicine*. 1999, Mosby, St Louis, *An essential resource for those seeking information beyond the brief summary presented in this text.*

MD Kittleson: Myxomatous atrioventricular valvular degeneration. In MD Kittleson, RD Kienle (Eds.): *Small animal cardiovascular medicine*. 1998, Mosby, St Louis, *A comprehensive, detailed description of degenerative valve disease in the dog; an excellent source for a more detailed description of MVD than that presented here*.

C Kvart, J Haggstrom, HD Pedersen, et al.: Efficacy of enalapril for prevention of congestive heart failure in dogs with myxomatous valve disease and asymptomatic mitral regurgitation. *J Vet Intern Med*. **16**, 2002, 80, *A landmark article that surprised the veterinary community and brought under scrutiny the widespread use of ACE inhibitors in patients with MVD before the onset of congestive heart failure*.

MW Miller, D Sisson: Infectious endocarditis. In PR Fox, D Sisson, NS Moise (Eds.): *Textbook of canine and feline cardiology*. ed 2, 1999, Saunders, Philadelphia, *An essential resource for those seeking information beyond the brief summary presented in this text.*

D Sisson, C Kvart, PG Darke: Acquired valvular heart disease in dogs and cats. In PR Fox, D Sisson, NS Moise (Eds.): *Textbook of canine and feline cardiology*. ed 2, 1999, Saunders, Philadelphia, *A comprehensive, detailed description of degenerative valve disease in the dog and an excellent source for a more detailed discussion of MVD than that presented here*.

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* See the CD-ROM for a complete list of references.

40 Chapter 40 Myocardial Contusion

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40.1 KEY POINTS

- Myocardial injuries often are overlooked in the trauma patient.
- The most common physiologic consequence of myocardial injury in dogs and humans is arrhythmias.
- Arrhythmias associated with myocardial injury may be delayed in onset up to 48 hours.
- Holter monitoring or continuous electrocardiographic (ECG) monitoring should be considered in high-risk patients.
- Troponins, cardiac-specific proteins, are an effective biomarker of myocardial injury in dogs.
- Normal ECG findings and cardiac troponin I levels on admission in traumatized human patients are an efficient way to rule out myocardial injuries and arrhythmias associated with trauma.
- Management of myocardial injuries is aimed toward maintaining optimal cardiac output and suppressing life-threatening arrhythmias.
- The class I antiarrhythmic agents, including lidocaine and procainamide, are used commonly to manage ventricular ectopy associated with myocardial injury.

40.2 INTRODUCTION

Traumatic myocarditis is a controversial subject. Much of the controversy in human studies revolves around a lack of consistent evidence that this injury has any effect on patient outcome and the expense associated with diagnostic testing, cardiac monitoring, and prolonged hospital stays.[1] Additional controversies associated with this injury revolve around its name, incidence, and how it is diagnosed. What appears to be agreed on consistently in the literature is the basic definition of this injury and that there is lack of an antemortem diagnostic gold standard. Direct visualization of the heart or histologic examination of damaged myocardium are considered the current diagnostic gold standard.[2]

The term *traumatic myocarditis* has been used frequently in veterinary literature to describe an assumed myocardial injury associated with arrhythmias in patients suffering from blunt thoracic trauma.[3] This term is used interchangeably with myocardial injury in this chapter.

40.3 INCIDENCE

Blunt thoracic trauma has been reported to result in myocardial injuries in 8% to 95% of human patients.[3-10] Reported variations in the frequency of myocardial injuries of dogs are similar to those described in humans. Several studies (three prospective, two retrospective) have examined the prevalence of traumatic myocarditis in the dog and report a range from 10% to 96%.[4,11-14] Variations in study design as well as disagreements regarding terminology, diagnostic modalities, and criteria used to identify myocardial injuries in humans and dogs contribute to the wide range in the reported frequency of this type of injury in both the human and veterinary literature.[2,3,7,13-21] The authors of these studies do agree, however, that myocardial injuries are easily overlooked.[18]

[*] References 2, 3, 7, 13–17, 20, 21.

40.4 ETIOLOGY, MECHANISM OF INJURY, AND PATHOPHYSIOLOGY

Thoracic trauma is common in dogs injured by automobiles, animal attacks (bites, kicks), and falls from a height.[2,3,11-13,19-21] Because of the elastic nature of the thoracic cage, blunt trauma may subject the myocardium to compressive and concussive forces.[13,14,22-24] The most common mechanism of myocardial injury in the dog is that secondary to lateral chest compression.[22,24] In addition to potential concussive injury from forceful contact with the ribs, sternum, and vertebrae when rapid acceleration or deceleration occurs, it has been proposed that distortion of the thoracic cage results in a rise in intrathoracic and intracardiac pressures, causing shearing stresses within the myocardium powerful enough to result in contusions.[6]

In vivo studies performed in dogs to mimic blunt chest trauma have correlated histopathologic areas of myocardial injury with areas of injury found during echocardiographic examination. Experimental trauma delivered to the left side of the chest resulted in abnormalities that were located primarily in the craniolateral wall of the left ventricle, and right-sided chest trauma produced septal and right ventricular wall damage.[6]

Gross pathologic findings in the traumatized heart have been characterized by localized edema, ecchymosis, and intramyocardial hematoma formation. Myocardial injuries were often transmural, with the epicardial surface being more severely affected.[6]

Arrhythmias and conduction defects are the most commonly reported consequences of myocardial injuries in humans and dogs.[7,11,22-27] One proposed proarrhythmic mechanism of myocyte trauma is the lowering of the ratio of effective refractory period to action potential duration and an increase in the resting membrane potential (less negative) in damaged myocardial cells. Additionally it is proposed that myocyte injury results in alterations of sodium and calcium currents across cell membranes, increasing the availability of intracellular calcium, resulting in increased sensitivity to depolarization.[3] These proposed intracellular derangements secondary to trauma can 171 potentiate 172 arrhythmogenesis.[3] Arrhythmias become apparent when the injured myocardium becomes the site of the most rapid impulse formation, overcoming the sinus node as the dominant (overdrive) pacemaker. The injured myocardium becomes the new overdrive pacemaker, propagating the arrhythmia by depolarizing the sinus node before it has a chance to fire and recapture the cardiac rhythm.[3]

Isolated rabbit hearts have been subjected to injury during high-resolution mapping of epicardial excitation to identify the origin of arrhythmias in injured myocardium. The results of this study identified reentry as the mechanism of arrhythmia due to myocardial contusion. The authors found that the site of impact became electrically silent (temporarily), resulting in a fixed and functional conduction block that caused reentry initiation.[28]

Traumatized patients may also develop arrhythmias associated with metabolic acidosis, hypoxia, electrolyte imbalance, intracranial injuries, and catecholamine release.[23,25-27,29] These physiologic aberrations all promote alterations in membrane transport and permeability of cations (sodium, potassium, and calcium), which lead to a decrease in resting membrane potential, as described earlier, contributing to aberrant depolarization and arrhythmias.[3,23,25]

The most frequently reported arrhythmias secondary to canine myocardial injuries include premature ventricular contractions, ventricular tachycardia, and nonspecific ST segment elevation or depression.[6,22-27,29] Less commonly reported arrhythmias reported in dogs with chest trauma include atrial fibrillation, sinus arrest with ventricular or junctional escape complexes, and second-degree and third-degree atrioventricular block.[7,12,22,27]

40.5 DIAGNOSIS

Although uncommonly performed in the live patient, gross or histologic examination of the heart remains the diagnostic gold standard for myocardial contusions.[2,17,30] Because of the impracticality of visualizing the heart or performing myocardial biopsy, an understanding of the mechanism of injury, an awareness of associated injuries, and a high index of suspicion for myocardial injury are essential in making a diagnosis.[10] Emergency clinicians should consider myocardial injury in all traumatized dogs that have the following injuries: (1) fractures of extremities, spine, or pelvis, (2) external evidence of thoracic trauma, (3) radiographic evidence of chest trauma such as pulmonary contusions, pneumothorax, hemothorax, diaphragmatic rupture, and rib or scapular fractures, and (4) neurologic injury.*

Dogs with any of these injuries should have a lead II electrocardiograph (ECG) performed and, depending on the patient's condition and the clinician's index of suspicion, the ECG should be repeated intermittently (i.e., every 2 to 24 hours). ECG abnormalities commonly are delayed in onset for up to 48 hours after blunt chest trauma, so in cases in which there is a high index of suspicion for myocardial injury ECG monitoring should be considered for that time frame.[22,23,25] Holter monitoring is the most sensitive and least invasive indicator of arrhythmias in dogs with suspected myocardial injuries. However, the lack of immediate Holter interpretation (rapid turnaround time) may limit the practical application of this modality for veterinarians.[12] Other forms of continuous ECG monitoring, such as single patient monitors and telemetry, would likely provide a similar advantage over intermittent ECGs without the delays in interpretation encountered with Holter monitoring.[18]

An echocardiogram should be considered in severely traumatized dogs with a poor response to resuscitative efforts and evidence of thoracic injuries even if no ECG abnormalities are present. Transthoracic echocardiography in the dog can be used to identify and localize both structural and functional abnormalities of injured myocardium due to blunt chest trauma. The echocardiographic features of myocardial injuries in the dog include (1) increased end-diastolic wall thickness, (2) impaired contractility, indicated by wall motion abnormalities and decreased fractional shortening, (3) increased echogenicity, and (4) localized areas of echolucency consistent with intramural hematomas.[6]

Serum myocardial isoenzyme analysis (cardiac troponins T and I [cTnT and cTnI]) has been used to diagnose myocardial injury in dogs and humans. The skeletal isoforms of the troponin proteins expressed are different from those in cardiac muscle.[19,31] The troponin structure is highly conserved across many differing species, allowing for veterinary application of tests currently in use at human care facilities.[32]

Troponin testing is based on immunologic detection of the cardiac-specific isoforms of troponin T and troponin I.[31] In both human and dogs, detectable levels appear in the circulation within 4 to 6 hours of cardiac myocyte injury, and serum elevations may be present for up to 7 days.[7,19,32] In a comparison of multiple myocardial enzyme and protein markers and ECG to detect myocardial injury in traumatized dogs, cTnI was the most sensitive indicator of this type of injury.[2] One of the most important findings of the many human studies investigating the clinical use of cardiac troponins appears to be the negative predictive values for cardiac complications in trauma patients. In human trauma patients a normal cTnI level in combination with a normal ECG tracing on arrival has a negative predictive value of 100% for myocardial injuries, allowing these patients to avoid intensive cardiac monitoring and even be discharged safely in the absence of other significant injuries.[33] Because of the controversies and difficulty diagnosing myocardial injuries in dogs, veterinarians should consider using these two tests to rule out this disease in a quick and practical manner. Although there are no studies confirming this hypothesis in dogs, clinicians could consider performing a baseline ECG and cTnI measurement within 4 hours of injury. Extrapolating from human findings, dogs with a combination of normal ECG findings and cTnI levels (normal <0.03 to 0.07 ng/ml[34]) would be less likely to develop arrhythmias and therefore would not require intensive cardiac monitoring. A positive finding on either test would suggest the possibility of myocardial injury and would indicate continuous ECG monitoring in those dogs.

* References 2, 12, 22, 25, 29, 30.

40.6 TREATMENT

Treatment of myocardial injuries typically is aimed at suppressing potentially life-threatening arrhythmias and maintaining adequate tissue perfusion.[30] Antiarrhythmic therapy is not recommended if arterial pulse quality is good and synchronous on auscultation, mean arterial pressure is higher than 75 mm Hg, mucous membranes are pink, capillary refill time is 2 seconds or less, and the patient has no clinical signs of weakness or cardiopulmonary distress.[30] Antiarrhythmic therapy should be considered when properly stabilized patients (i.e., received adequate fluids, electrolytes, oxygen, pain control) develop arrhythmias such as multiform premature ventricular complexes, ventricular tachycardia, and the R-on-T phenomenon.[23,26,27,30] Treatment is imperative when arrhythmias are accompanied by clinical evidence of decreased cardiac output such as hypotension, weakness, pale mucous membranes, delayed capillary refill time, collapse, or syncope.[23,26,30] Additionally, treatment is indicated when an arrhythmia has a sustained (>15 to 30 seconds) ventricular rate that exceeds 140 to 180 beats/min in the dog.[12,23,26]

Lidocaine (2 mg/kg IV bolus) is the agent of choice for traumatized dogs suffering from ventricular ectopy fulfilling the criteria described in the previous paragraph.[30] Intravenous boluses of lidocaine may be repeated every 10 to 20 minutes until a cumulative dose of 8 mg/kg is given. A constant rate infusion (CRI) of 40 to 80 μg/kg/min may be initiated to maintain a cardiac rate and rhythm that provides appropriate tissue perfusion.[23,30] Additional boluses of lidocaine are often required to suppress arrhythmias while steady-state blood levels are achieved by the CRI. The upper end of the recommended dosages of lidocaine may cause vomiting or seizures, so administration should be slowed or temporarily discontinued if these signs develop.[23,30,35]

If lidocaine does not resolve ventricular ectopy, procainamide may be administered intravenously or intramuscularly (6 to 15 mg/kg q4-6h).[23,30] If repeated boluses of procainamide are required to suppress arrhythmias, a CRI (10 to 40 μg/kg/min) may be started. Oral procainamide (sustained release formulation 20 mg/kg q8h) may be initiated if continued management is required and oral medications can be tolerated. Potential side effects of procainamide administration include hypotension and atrioventricular conduction block.[23,35] Additional oral arrhythmia management options include tocainide (10 to 20 mg/kg PO q8-12h) and mexiletine (4 to 8 mg/kg PO q8h).[23] The reported side effects of tocainide include nausea, vomiting, and anorexia; although less frequently observed, complications associated with mexiletine include excitement or depression.[35]

β-Blockers (propranolol, metoprolol, atenolol, sotalol) should be considered cautiously when traumatized dogs with ventricular ectopy are unresponsive to class I antiarrhythmic agents, have been treated appropriately for shock and pain, and are not receiving positive inotropic medications.[30,35] An ultrashort-acting intravenous β-blocker, such as esmolol, may be used to test the efficacy of β-blockers in managing ventricular arrhythmias that have not responded to other medications.[26] The potential for serious side effects such as atrioventricular block, hypotension, bronchoconstriction, and decreased cardiac contractility must be considered when using β-blockers. [23,35]

Arrhythmias secondary to myocardial trauma that do not fulfill the stated guidelines for management are likely to be self-limiting and resolve within 3 to 10 days.[30] The end point of therapy is not necessarily complete resolution of the arrhythmia; appropriate therapeutic response includes reduction of the heart rate (<140 beats/min) and the return of adequate tissue perfusion.[30] In most cases antiarrhythmic therapy can be discontinued within 48 to 72 hours; however, it is recommended that intermittent ECG monitoring continue up to 1 week after discharge.[30] Medications being used to suppress arrhythmias should be discontinued a minimum of 24 hours before reexamination.[30] The most sensitive way to detect complete resolution of arrhythmias after discontinuing antiarrhythmic medications is continuous ECG (Holter) monitoring.[12] If some form of continuous monitoring is not available, intermittent lead II ECG monitoring can be performed to ensure that the arrhythmia has resolved and it is safe to discontinue therapy. If the arrhythmia persists, long-term oral therapy may be initiated.[30]

If a dog with a suspected myocardial injury must undergo anesthesia, agents that are least likely to induce arrhythmias, such as acepromazine, butorphanol, isoflurane, and glycopyrrolate, should be used.[3,23] Halothane, atropine sulfate, and the thiobarbiturates should be avoided because they are reported to exacerbate arrhythmias and to sensitize the heart to catecholamine-induced arrhythmias.[23,25]

40.7 SUMMARY

Although myocardial injuries may cause significant alterations in cardiac function in the traumatized dog, they are often overlooked in the face of severe trauma. Ventricular arrhythmias are the most common abnormalities caused by blunt myocardial injury. Although ECG monitoring traditionally has been used to diagnose myocardial injuries, the onset of arrhythmias associated with these injuries is often delayed, making recognition difficult. Arrhythmias may be secondary to alterations in transport of cations, such as calcium, potassium, and sodium, across the membranes of injured myocytes, resulting in a decrease of resting membrane potential, aberrant firing of injured cells, and loss of organized myocyte depolarization or reentry mechanisms.

The medical community has yet to provide a prospective study that investigates the need for therapeutic intervention of traumatic myocardial injuries in humans or dogs. Although newer noninvasive tests for myocardial injuries such as troponin levels may assist in diagnosing these injuries, they have not yet proven to be the single noninvasive diagnostic modality to detect myocardial injury.[18] In the real world of veterinary practice, continuous ECG monitoring has been shown to be a sensitive, noninvasive indicator of arrhythmias in traumatized dogs and should be considered in dogs with suspected myocardial injuries.[12]

A human study may have inadvertently stumbled upon an approach that makes more sense than those previously discussed, ruling out this disease rather than ruling it in. This study showed that in traumatized patients a combination of normal ECG and cTnI findings on admission had a 100% negative predictive value for cardiac complications, meaning that none of the patients with these test results developed arrhythmias requiring intervention.[33] These findings may be helpful in determining the need for continuous ECG monitoring in canine patients with suspected myocardial trauma and should be considered for further investigation in dogs.

40.8 SUGGESTED FURTHER READING*

JA Abbott: Traumatic myocarditis. In JD Bonagura (Ed.): *Kirk's current veterinary therapy*. ed 13, 2000, Saunders, Philadelphia, *A textbook summary of traumatic myocarditis*. 173

174 P Mucha: Blunt myocardial injury (myocardial contusion). In JL Cameron (Ed.): *Current surgical therapy*. ed 8, 2004, Mosby, St Louis, *A thorough human textbook summary of both controversies involving this injury and the injury itself*.

RR Paddleford: In *Anesthetic considerations for the high-risk patient requiring a short anesthetic procedure*. AAHA Scientific Proceedings, Denver, March 25-29 1995, *A good review of commonly used anesthetic agents and their pharmacokinetics as well as their effects on the cardiovascular and pulmonary systems*.

AJ Reiss, BC McKiernan: Myocardial injury secondary to blunt thoracic trauma in dogs: diagnosis and treatment. *Comp Cont Educ Pract Vet*. **24**, 2002, 944, *A review paper that provides a diagnostic and management algorithm for myocardial injuries*.

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* See the CD-ROM for a complete list of references.

41 Chapter 41 Myocardial Infarction

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41.1 KEY POINTS

- Myocardial infarction is relatively uncommon in small animal patients.
- Myocardial infarction can be associated with primary cardiovascular disease or can be secondary to other systemic disease processes.
- Antemortem diagnosis is challenging and is based on certain clinical pathologic derangements and electrocardiographic (ECG) and echocardiographic changes.
- Management is largely supportive to help maintain cardiac perfusion, suppress arrhythmias, and manage the underlying causes of the infarction or ischemia.

41.2 INTRODUCTION

Myocardial infarction is the end result of either acute or chronic myocardial ischemia. Myocardial ischemia differs slightly from myocardial hypoxia in that ischemia results in a stasis of waste products of cellular metabolism in addition to a lack of oxygen delivery, leading to cellular damage above and beyond that from hypoxemia.[1] Myocardial infarction is a pathologic diagnosis and, depending on whether it is acute or chronic, is characterized by loss of normal cardiac myocyte structure (i.e., myocytolysis, coagulative necrosis, inflammatory cell infiltration, and fibrosis). Myocardial infarction has a host of causes and is a leading cause of cardiovascular disease and death in humans.[2] The vast majority of myocardial infarction in people stems from coronary artery disease and atherosclerosis, both of which are relatively uncommon in the veterinary patient population. In dogs, collateral circulation of the coronary arterial supply is relatively extensive,[1] so the probability of irreversible myocardial ischemia from any one coronary arterial occlusion may be lower in this species.

The clinical manifestations of myocardial ischemia and infarction in veterinary patients can range from nonspecific symptoms to severe life-threatening arrhythmias and congestive heart failure. Thus, clinical suspicion of myocardial infarction should lead to aggressive management and supportive care. Prognosis depends on the severity of clinical signs, presence of concurrent disease, and response to initial therapy.

41.3 ASSOCIATED DISEASE PROCESSES

Multiple extracardiac disease processes have been associated with myocardial infarction in dogs and cats. In theory, any disease that induces a hypercoagulable state or thromboembolic complications can increase the risk of myocardial infarction. These include, but are not limited to, neoplasia, immune-mediated hemolytic anemia, trauma, heatstroke, loss of antithrombin III through renal or gastrointestinal disease, excess circulating corticosteroids (exogenous or endogenous), systemic inflammatory response syndrome, and sepsis. Atherosclerosis, a primary risk factor for infarction in humans, has been documented in dogs with hypothyroidism and diabetes mellitus.[3,4] In one study of 21 dogs with pathologically confirmed atherosclerosis, all had disease of the coronary arteries as well as fibrotic changes in the myocardium.[3] In another study, 20 of 30 dogs with atherosclerosis had coronary artery involvement.[4] Not all dogs with coronary atherosclerosis had clinical signs suggestive of cardiovascular disease, and of seven dogs that had ECG monitoring, only four had abnormalities.[3] This suggests that not all myocardial infarctions are clinically apparent.

Myocardial infarction can also be associated with primary cardiovascular disease. Bacterial endocarditis has been associated with myocardial infarction because emboli are showered from an infected valve and may lodge in the coronary arterial circulation.[5,6] Feline hypertrophic cardiomyopathy can lead to myocardial infarction through several different mechanisms. First, an increased oxygen demand of the hypertrophied ventricle can lead to chronic myocardial ischemia, especially in the endocardium. It has been hypothesized that this myocardial ischemia or infarction may lead to fatal ventricular arrhythmias and sudden death in some cats with hypertrophic cardiomyopathy. Second, decreased oxygen delivery to the hypertrophied ventricle results in proliferative remodeling of the coronary arterioles and obliteration of the vessel lumen.[7,8] Furthermore, cats with hypertrophic cardiomyopathy develop diastolic dysfunction, which leads to elevated left ventricular filling pressures and eventual left atrial dilation. It is thought that left atrial dilation, via altered hemodynamics and blood pooling, is a predisposing factor for thrombus formation, and this may lead to microthrombi that embolize to the coronary circulation, and result in myocardial infarction. Lastly, cats with significant hypertrophic cardiomyopathy may be persistently tachycardic, and as the ratio of time spent in systole versus diastole increases, diastolic flow into the coronary circulation is impaired, leading to myocardial hypoxia. Dogs with subaortic and pulmonic stenosis are thought to be at higher risk for myocardial infarction for reasons similar to those in cats with hypertrophic cardiomyopathy.[9-11] Dogs with cardiac neoplasia and chronic valvular disease also can have myocardial infarction.[11,12]

41.4 HISTORY AND CLINICAL SIGNS

Clinical signs in dogs and cats with myocardial infarction range from nonspecific to sudden death.[13] In one study, the most common initial signs in dogs and cats with histopathologically confirmed acute myocardial infarction were lethargy and inappetence.[14] In another study, 20% of dogs with infarctions experienced sudden death as the first manifestation.[15] The lack of specificity of clinical signs can make myocardial infarction difficult to diagnose. If present, more specific signs, such as dyspnea, collapse, and syncope, are largely attributable to and compatible with primary cardiac disease. These commonly are seen with many forms of nonischemic organic heart disease, so further investigation is necessary to evaluate specifically for myocardial infarction.

41.5 PHYSICAL EXAMINATION

The most commonly reported physical examination findings in dogs with myocardial infarction are dyspnea, tachycardia, arrhythmias, cardiac murmurs, and signs attributable to other concurrent systemic disease. Information is limited in cats; however, dyspnea and tachycardia have been reported. Dyspnea often is related to congestive heart failure (i.e., pulmonary edema or pleural effusion) or pulmonary thromboembolism. Arrhythmias can range from single premature supraventricular and ventricular beats to supraventricular tachycardias, atrial fibrillation, and ventricular tachycardia. The rhythm likely is determined by the location and extent of damaged myocardium. Murmurs, if present, probably arise from primary cardiac disease, rather than from myocardial infarction per se.

41.6 DIAGNOSTIC WORKUP

In veterinary patients, antemortem diagnosis of myocardial infarction is challenging because there are no established diagnostic criteria. The diagnostic workup typically includes diagnostic imaging in addition to clinicopathologic, and electrophysiologic tests. Clinicopathologic diagnostics include a complete blood count, serum chemistry panel, urinalysis, thyroxine level, coagulation panel, D-dimer levels, thromboelastography, and cardiac troponin I (cTnI) levels. Common derangements include elevated aspartate aminotransferase, alanine aminotransferase, creatine kinase, and cTnI values. Coagulation parameters outside of the reference ranges may increase the index of suspicion.

Because of a high degree of sensitivity and specificity, cTnI is considered a gold standard test in the diagnosis of myocardial infarction in humans. cTnI values above the 99% reference limit and accompanied by pathologic ECG changes or appropriate clinical signs (i.e., angina, syncope) are indicative of recent infarction.[16] In dogs with experimentally induced myocardial infarction, cTnI values are elevated dramatically, up to 150 times the upper reference range, and can remain up to 25 times the upper reference range for 4 days or longer.[17] Elevated cTnI values have been reported in normal dogs and cats, as well as in patients with a variety of naturally occurring heart diseases (i.e., dilated cardiomyopathy, hypertrophic cardiomyopathy, subaortic stenosis, mitral valve disease).[18-24] In many of these cases, mild elevations of cTnI likely reflect myocardial hypoxia and ischemia secondary to underlying disease, rather than myocardial infarction per se. We postulate that antemortem diagnosis of acute myocardial infarction in veterinary species would involve greatly elevated cTnI values detectable within 24 hours of the index event. In theory and in the absence of repeated infarction events, cTnI values should slowly decrease back toward baseline over several days to weeks. Additional clinical pathologic abnormalities associated with underlying disease processes, such as proteinuria and azotemia in animals with glomerular and tubular renal disease, or low thyroxine in dogs with hypothyroidism, may also be present.

An ECG should be performed in any animal in which myocardial infarction is suspected. The most common arrhythmia is sinus tachycardia, followed by ventricular tachycardia, atrial fibrillation, and ventricular premature complexes. Elevation or depression of the ST segment, prolonged QT interval, or T wave abnormalities may also suggest myocardial hypoxia or ischemia. Based on a very limited number of reports, ECG findings in cats may include ventricular premature complexes and atrial fibrillation.[14,25] As opposed to humans, strict ECG criteria for diagnosis of myocardial infarction in veterinary species do not exist.

Diagnostic imaging, including thoracic radiographs and echocardiography, should be performed in animals with suspected myocardial infarction. Thoracic radiographs may show cardiomegaly associated with primary cardiac disease. Signs of congestive heart failure may be present, including pulmonary venous congestion, pulmonary edema, or pleural effusion. Echocardiography can detect underlying cardiac disease that may predispose to myocardial infarction (i.e., hypertrophic cardiomyopathy, subaortic stenosis). Cardiac ultrasonography may detect regional or global hypokinesis, regional myocardial hyperechogenicity, poor systolic function, and cardiac chamber enlargement or aneurysms. Visualization of intracardiac thrombi heightens the suspicion for myocardial infarction. Confirmation of myocardial infarction is made postmortem via gross and histopathologic examination.

41.7 TREATMENT

Treatment of myocardial infarction is predominantly supportive. Control of arrhythmias with appropriate antiarrhythmic agents, diuresis for congestive heart failure, and oxygen therapy form the basis of treatment. 175 Administration of β-blockers and angiotensin-converting enzyme inhibitors is common in humans with acute 176 myocardial infarction and helps reduce myocardial oxygen demands and ameliorate pathologic remodeling. The benefit of these treatments in dogs and cats is unknown; however, β-blocker use should probably be limited to patients with adequate systolic function. In humans, the use of fibrinolytics, such as tissue plasminogen activator, is generally reserved for the acute period (within 12 hours after the primary event) and is accompanied by a small risk for cerebral hemorrhage and other bleeding complications (see Chapter 188, Thrombolytic Agents). Antiplatelet and antithrombin therapy with aspirin or heparin may be helpful, particularly in patients with intracardiac thrombi (see Chapter 187, Anticoagulants). Recognition and management of any underlying disease process are indicated, including thyroid supplementation for hypothyroid dogs, regulation of diabetes mellitus, and control of any systemic inflammation or disease that may be precipitating a hypercoagulable state.

41.8 PROGNOSIS

Prognosis for animals with severe acute myocardial infarction is poor. Because diagnosis is difficult, it is likely that myocardial infarction is an under recognized phenomenon in the veterinary patient population. The prognosis is largely dependent on the severity of clinical signs, the underlying disease process, and the response to therapy.

41.9 SUGGESTED FURTHER READING*

S Driehuys, TJ Van Winkle, CD Sammarco, KJ Drobatz: Myocardial infarction in dogs and cats: 37 cases (1985-1994). *J Am Vet Med Assoc*. **213**, 1998, 1444, *A retrospective study investigating the incidence and associated clinical and pathologic findings of myocardial infarction in cats and dogs*.

S Liu, PR Fox: Myocardial ischemia and infarction. In JD Bonagura (Ed.): *Kirk's current veterinary therapy XIII*. ed 13, 2000, Saunders, Philadelphia, *A review of the etiology, pathology, and clinical diagnosis and management of myocardial infarction in veterinary patients*.

KE Schober, B Kirbach, C Cornand, G Oechtering: In *Cardiac troponins in small animals*. Proceedings of the Nineteenth Annual ACVIM Forum, Denver, May 22-24 2001, *A report on the clinical entities that may result in an elevation of cardiac troponin levels in veterinary patients, including trauma, cardiomyopathy, myocarditis, pericarditis, gastric dilation and volvulus, doxorubicin toxicity*.

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* See the CD-ROM for a complete list of references.

42 Chapter 42 Hypertensive Crisis

Scott Brown, VMD, PhD, Diplomate (ACVIM)

42.1 KEY POINTS

- Emergency antihypertensive therapy is indicated only when there is end-organ damage likely to produce significant permanent abnormalities without rapid lowering of blood pressure (BP).
- Diagnosis and management of hypertension must be based on measurement of the patient's BP following a standard protocol, and a thorough physical examination should be performed concurrently to assess end-organ damage.
- The primary goal of emergency antihypertensive therapy is to reduce the magnitude, severity, and likelihood of further end-organ damage.
- To resolve a hypertensive crisis, systolic BP should be lowered to 110 to 150 mm Hg, generally within 4 to 12 hours, using parenteral or oral pharmacologic agents.

42.2 RATIONALE FOR EMERGENCY MANAGEMENT

Elevations of systemic arterial BP can injure tissues, referred to as *end-organ damage*. The end organs affected by elevated BP include the kidney, cardiovascular system, eye, and brain. A hypertensive crisis mandating emergency therapy occurs whenever there is end-organ damage that is likely to produce significant permanent abnormalities unless BP is lowered immediately. In veterinary patients, the end organs affected by this type of damage are usually the eyes and brain (Table 42-1).

42.3 END-ORGAN DAMAGE

42.3.1 Ocular

Ocular lesions are observed in many animals with systemic hypertension; reported prevalence rates are as high as 100%.[1-6] The syndrome of hypertensive ocular injury is most often termed *hypertensive retinopathy*. [2,4,7,8] Sudden onset of blindness, intraocular hemorrhage, and retinal detachment are the most common indications for emergency lowering of BP. Other ocular lesions associated with high BP include retinal vessel tortuosity, edema, and retinal degeneration. Effective antihypertensive management can lead to retinal reattachment, although restoration of vision is not common and subsequent retinal degeneration leading to blindness may occur. Hypertensive ocular injury has been reported at systolic BP as low as 168 mm Hg,[3] and there is a substantially elevated risk of occurrence when systolic BP exceeds 180 mm Hg, particularly when this occurs suddenly.[6,8]

42.3.2 Neurologic

Neurologic clinical signs are frequently in hypertensive dogs and cats. Signs include altered mentation, disorientation, lethargy, seizures, balance disturbances, head tilt, nystagmus, behavioral abnormalities, and focal neurologic defects. Hypertensive encephalopathy[9] is a complication justifying rapid lowering of BP that has been reported in dogs[5] and cats,[4,7,10,11] occurring as a well-described entity in humans characterized by white matter edema and vascular lesions.[12] Hypertensive encephalopathy also occurs after renal transplantation in humans[13] and is a cause of otherwise unexplained death in cats.[10] Hypertensive encephalopathy is more likely to occur with a sudden rise of BP or a systolic BP that exceeds 180 mm Hg.[14] This syndrome, in its early phases, is rapidly responsive to lowering of BP.[10,14] Hemorrhagic and ischemic stroke are observed in dogs and cats, and these conditions may generally be distinguished from hypertensive encephalopathy by virtue of their slow and incomplete response to lowering BP. Before treating hypertension in the patient with evidence of intracranial disease, a Cushing reflex in response to increased intracranial pressure must be distinguished from neurologic injury secondary to hypertension (see Chapter 100, Intracranial Hypertension).

42.3.3 Renal

In the kidney, hypertensive injury generally manifests as an enhanced rate of decline of renal function, early renal death, and proteinuria. Proteinuria is a marker of hypertensive nephropathy in humans,[15] and severity was directly related to degree of elevation of BP in an experimental study of chronic kidney disease in cats.[14] Malignant hypertension is a syndrome of severe, progressive elevations of BP causing end-organ damage that is often associated with kidney disease and is a recognized cause of rapidly progressive renal injury in rats and people, necessitating quick reductions in BP. However, hypertensive damage to the canine and feline kidneys is almost always a slow and insidious process requiring weeks to years to fully manifest, and is thus rarely a rationale for emergency therapy in dogs and cats.

Table 42-1 Hypertensive End-organ Damage

End Organ	Hypertensive Injury	Clinical Findings	Can this damage be a rationale for emergency antihypertensive therapy?
Eye	Retinopathy	Acute blindness, retinal detachment, or hemorrhage	Yes
	Choroidopathy	Vitreal hemorrhage or hyphema	
Brain	Encephalopathy	Central neurologic symptoms of acute onset	Yes
	Stroke		
Kidney	Progression of chronic kidney disease	Serial increases in serum creatinine concentration	Generally, no
		Proteinuria	
Heart and vessels	Cardiac failure	Left ventricular hypertrophy	Generally, no
		Systolic murmur	
		Arrhythmias	
		Evidence of cardiac failure	

42.3.4 Cardiovascular

Cardiac changes in hypertensive animals may include systolic murmurs and cardiac gallops[16] and left ventricular hypertrophy.[1,4,16,17] Although cats with previously undiagnosed hypertension may unexpectedly develop signs of congestive heart failure after receiving fluid therapy, heart failure and other serious complications are infrequent[4,7,18] and slow to develop. Although vascular injury within the eye or central nervous system is a rationale for emergency therapy, cardiac changes rarely mandate rapid reductions in BP.

42.4 PATIENTS AT RISK FOR HYPERTENSION

There are at least two primary indications for evaluating BP in a patient. First, BP should be measured in patients with clinical abnormalities consistent with hypertensive end-organ damage; the presence of unexplained clinical findings that are associated with systemic hypertension should lead to BP measurement at the time of diagnosis. For emergency treatment, this generally includes clinical signs of hypertensive retinopathy or hyphema and unexplained intracranial neurologic signs (e.g., seizures, altered mentation, focal neurologic deficits). A second indication for BP measurement is the presence of diseases or conditions casually associated with secondary hypertension (e.g., chronic kidney disease, feline hyperthyroidism, diabetes mellitus, and hyperadrenocorticism) or the use of therapy that may elevate BP (e.g., sympathetic agonists or intensive fluid therapy). A thorough physical examination, including funduscopic evaluation, cardiac auscultation, and neurologic examination, should concurrently be performed in these at-risk populations to assess for end-organ damage. Abnormalities of the urinary (e.g., microalbuminuria, proteinuria, azotemia, or structural changes in the kidney) and cardiovascular (e.g., unexplained left ventricular hypertrophy, gallop rhythm, arrhythmia, or systolic murmur) systems also indicate BP measurement.

42.5 MEASUREMENT OF BLOOD PRESSURE

Diagnosis and treatment of hypertension must be based on the patient's BP. It can be measured directly by an intraarterial means[19] or indirectly by devices employing a compressive cuff. Arterial puncture by needle or catheter has been used in veterinary medicine.[7] Radiotelemetric implants have been employed in laboratory studies of hypertension in dogs[20] and cats,[14,21-24] and this technology may yet prove to be a clinically useful approach. However, indirect devices are generally more clinically acceptable and in much wider use[9,25-32] (see Chapters 49 and 203, Arterial Catheterization and Hemodynamic Monitoring, respectively).

Diagnosis and treatment of hypertension generally are based on systolic BP. This is largely because the risk of end-organ damage is most closely related to systolic BP in humans and rats. Furthermore, some devices commonly used in veterinary medicine do not provide reliable measurements of diastolic BP. Although isolated diastolic hypertension (elevated diastolic with normal systolic BP) occurs in dogs and cats, animals with end-organ damage necessitating rapid BP reductions should be expected to exhibit elevations of both systolic and diastolic BP.

To obtain reliable values, it is important to follow a standard protocol. The BP may be affected by stress or anxiety associated with the measurement process,[22] and these changes may result in a false diagnosis of hypertension.[33] This anxiety-induced, artifactual elevation of BP is often referred to as *white-coat hypertension,* a reference to the white coat of the medical professional measuring BP. A measurement session consisting of three to seven consecutive indirect measurements should be obtained before initiation of antihypertensive therapy. Although the general rule is to conduct at least two measurement sessions separated by 30 minutes or more before initiating therapy, the presence of ocular or neurologic end-organ damage constituting an emergency is an exception to this rule.

42.6 TREATMENT OF THE EMERGENCY HYPERTENSIVE PATIENT

Before making a decision to treat high BP as a hypertensive crisis, careful evaluation of the patient and appropriate selection of agents are mandatory.

42.6.1 Decision to Treat

High BP measurements alone do not constitute an emergency. Emergency antihypertensive therapy is indicated only when two conditions have been met.

First and foremost, there is end-organ damage likely to produce significant permanent abnormalities without rapid lowering of BP (i.e., hypertensive neurologic or ocular injury).

Second, the degree of BP elevation places the patient at moderate or severe risk of sustained or worsening injury in these end organs.[9] High BP measurements can be caused by measurement artifact (i.e., stress-induced, or white-coat, hypertension), occur in association with other disease processes that may elevate BP (i.e., secondary hypertension), or occur in the absence of evidence for other potentially causative disease processes (i.e., idiopathic hypertension). A decision to use antihypertensive therapy should be accompanied by identification and treatment of conditions that may complicate therapy, generally those that cause secondary hypertension.

Table 42-2 ACVIM System for Classification of Systolic Blood Pressure Levels in Dogs and Cats Based on Risk for Further End-organ Damage[9]

Risk Category	Systolic Blood Pressure (mmHg)	Risk of Further End-organ Damage
I	<150	Minimal
II	150–159	Mild
III	160–179	Moderate
IV	≥180	Severe

ACVIM, American College of Veterinary Internal Medicine.

NOTE: Therapeutic target is generally a systolic BP of 110 to 150 mm Hg.

In patients with end-organ damage consistent with hypertension that may progress rapidly (i.e., hypertensive retinopathy and hyphema or neurologic abnormalities associated with high BP or intracranial hemorrhage), it is appropriate to consider antihypertensive therapy on the basis of risk of developing subsequent end-organ damage (Table 42-2), with systolic BP of 160 to 180 mm Hg posing a moderate risk and systolic BP of 180 mm Hg or higher a severe risk.[9] Generally, the nature and course of end-organ damage, rather than the degree of BP elevation, will dictate the decision to rapidly reduce BP. For animals with systolic BP of 140 to 159 mm Hg that exhibit otherwise unexplained ocular or neurologic damage that is potentially attributable to hypertension, a short-term (3 to 7 days) trial of antihypertensive therapy may be cautiously employed.

42.6.2 Pharmacologic Agents

Once a decision is made to treat an animal with high BP, therapeutic intervention will generally be with a pharmacologic agent. Certain disease conditions identified during this evaluation may be best addressed with specific classes of agents, such as β-blockers for hypertension-associated hyperthyroidism, or α-blockers and β-blockers or surgical excision for pheochromocytomas, aldosterone receptor blockers or surgical excision of adrenal tumors in animals with hypertension associated with hyperaldosteronism, or some combination of calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone receptor blockers for hypertension associated with kidney disease in dogs.[9,14,34-37]

For emergency management, agents with a rapid onset of action are required. Cautious use of agents at reduced dosages is generally counterproductive and time consuming. Appropriate agents (Table 42-3)[9,38] include parenteral medications such as hydralazine, enalaprilat, labetalol, and esmolol, as well as those with rapid onset of effect when administered orally (e.g., amlodipine besylate). There is limited clinical information on the use of several of these agents for this purpose (e.g., esmolol). Hydralazine and amlodipine are employed most commonly. If medications are administered parenterally, continuous BP monitoring via arterial catheterization is strongly recommended. Many clinicians prefer oral calcium channel blockers, particularly in cats, because they generally lower BP in severely hypertensive animals within 4 to 6 hours irrespective of primary disease, and these agents carry a limited risk of causing hypotension or BP instability.

Table 42-3 Examples of Agents Used for Emergency Antihypertensive Therapy in Dogs and Cats*

Agent	Route	Dosage
Parenteral		
Hydralazine†	IV or IM	0.2 mg/kg, repeat q 2 hr as needed
Enalaprilat	IV	0.2 mg/kg, repeat q 1–2 hr as needed
Labetalol	IV	0.25 mg/kg over 2 minutes, repeat up to a total dosage of ≤3.75 mg/kg followed by a constant rate infusion of 25 μg/kg/min
Esmolol	IV	50–75 μg /kg/min constant rate infusion
Oral		
Amlodipine†	Oral	0.25 mg/kg q 24 hr; dosages up to 0.5 mg/kg q 24 h may be employed, albeit cautiously

IM, intramuscular; *IV,* intravenous.

* This list is not intended to be exhaustive; other antihypertensive agents may be appropriate.

† Most frequently employed agents.

42.6.3 Therapeutic Goals

The goal of antihypertensive therapy is to reduce the magnitude, severity, and likelihood of further end-organ damage, generally to reduce systolic BP to 110 to 150 mm Hg. Because end-organ damage is likely to be directly related to systolic BP and adversely affected by wide fluctuations in BP, it is preferable to achieve a stable reduction of BP to the lower half of this range. Some severely hypertensive animals (i.e., systolic BP >250 mm Hg) and those with secondary vascular changes may exhibit signs of hypotension (i.e., syncope, weakness, exercise intolerance, and prerenal azotemia) when BP is lowered rapidly. This is uncommon if the systolic BP is maintained above 110 mm Hg.

If an antihypertensive agent of choice is only partially effective, the usual approach is to consider increasing the dosage or adding an additional drug. Although not ideal, management of highly resistant hypertension in humans often requires more than three agents, and veterinary patients with severe hypertension often require more than one agent.

42.6.4 Follow-up

Measurement of BP and assessment for changes related to end-organ damage should be performed frequently, initially at least every 12 hours. Patients receiving parenteral antihypertensive agents should be assessed more frequently, generally at 1- to 3-hour intervals. Choice of agents, drug dosage, and dosage interval should be adjusted according to BP, with a goal of maintaining a stable systolic BP between 110 and 150 mm Hg without evidence of effects of low BP. It is important to carefully reevaluate any patient treated with emergency antihypertensive therapy before instituting further therapy. Follow-up evaluations should include measurement of BP, funduscopic examination, and other assessments specific to the individual's end-organ damage and concurrent diseases. Once end-organ damage and BP are stabilized, generally within 3 to 5 days, the transition to an oral antihypertensive regimen should be made gradually.

42.7 SUGGESTED FURTHER READING*

S Brown, C Atkins, R Bagley, et al.: Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. *J Vet Intern Med*. **21**, 2007, 542,(in press) *Extensive guidelines of the ACVIM Hypertension Consensus Pancl*.

J Elliott, PJ Barber, HM Syme, et al.: Feline hypertension: clinical findings and response to antihypertensive treatment in 30 cases. *J Small Anim Pract*. **42**, 2001, 122, *Review of end-organ damage and result of management of hypertension in spontaneous feline hypertension*.

F Jacob, DJ Polzin, CA Osborne, et al.: Association between initial systolic blood pressure and risk of developing a uremic crisis or of dying in dogs with chronic renal failure. *J Am Vet Med Assoc*. **222**, 2003, 322, *First clinical report to identify a link between high BP and progression of chronic kidney diseases in dogs*.

RE Jepson, J Elliott, D Brodbelt, et al.: Effect of control of systolic blood pressure on survival in cats with systemic hypertension. *J Vet Intern Med*. **21**, 2007, 542, *Report of posttransplant hypertensive encephalopathy and its management with emergency antihypertensive therapies*.

F Maggio, TC DeFrancesco, CE Atkins, et al.: Ocular lesions associated with systemic hypertension in cats: 69 cases (1985-1998). *J Am Vet Med Assoc*. **217**, 2000, 695, *Perhaps the most comprehensive report of hypertensive ocular injury. Provides a good overview of the clinical syndrome*.

* See the CD-ROM for a complete list of references

43 Chapter 43 Cardiac Tamponade and Pericardiocentesis

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43.1 KEY POINTS

- Cardiac tamponade occurs when intrapericardial pressure rises to equal or greater than normal cardiac filling pressure.
- The rate of pericardial fluid accumulation influences how quickly cardiac tamponade develops. A large pericardial fluid volume implies a gradual process.
- Cardiac tamponade is relatively common in dogs, but rare in cats.
- Clinical signs usually reflect poor cardiac output and systemic venous congestion.
- Right atrial collapse is a characteristic echocardiographic finding with cardiac tamponade.
- Immediate pericardiocentesis is indicated for cardiac tamponade.

43.2 INTRODUCTION

Normally, a small volume (≈0.25 ml/kg) of serous fluid lies between the outer fibrous (parietal) pericardial layer and the serous visceral pericardium or epicardium.[1] Excess, abnormal fluid within this space (pericardial effusion) is a common disorder that has a variety of causes (see Chapter 44, Pericardial Diseases). Pericardial effusion impairs cardiac function when intrapericardial pressure rises and prevents normal cardiac filling. Most pericardial effusions in dogs are serosanguineous or sanguineous; these are usually of neoplastic or idiopathic origin.[2,3] Pericardial transudates, modified transudates, and exudates occasionally occur in both dogs and cats.

43.3 PATHOPHYSIOLOGY OF CARDIAC TAMPONADE

The hemodynamic consequences of pericardial effusion depend on the intrapericardial pressure-volume relationship. Because the fibrous pericardium is relatively noncompliant, increases in fluid volume can sharply raise intrapericardial pressure. Cardiac tamponade develops when intrapericardial pressure rises toward and exceeds normal cardiac diastolic pressures.[2-4] The external cardiac compression progressively limits right ventricular filling and, with increasing severity, also reduces left ventricular filling.[2,3,5] Systemic venous pressure increases and forward cardiac output falls. Eventually, diastolic pressures in all cardiac chambers and great veins equilibrate.[2,3]

The rate of pericardial fluid accumulation and the distensibility of the pericardial sac determine whether and how quickly cardiac tamponade develops. Rapid accumulation of a relatively small-volume effusion (e.g., 50 to 100 ml) can raise intrapericardial pressure markedly, because pericardial tissue stretches slowly. Conversely, a slow rate of fluid accumulation may allow for enough pericardial enlargement to maintain low intrapericardial pressure until the effusion is quite large. A large volume of pericardial fluid implies a gradual process. So long as intrapericardial pressure is low, cardiac filling and output remain relatively normal and clinical signs are absent. Fibrosis and thickening further limit the compliance of pericardial tissue, and this can increase the likelihood of pericardial tamponade. Pericardial fibrosis and inflammatory cell infiltrates are described with idiopathic as well as neoplastic causes of effusion.[6,7]

Neurohormonal compensatory mechanisms are activated as cardiac output falls.[8,9] These contribute to fluid retention and other clinical manifestations of tamponade. Signs of systemic venous congestion become especially prominent over time. Although pericardial effusion does not directly affect myocardial contractility, reduced coronary perfusion during tamponade can impair both systolic and diastolic function. Low cardiac output, arterial hypotension, and poor perfusion of other organs besides the heart can ultimately precipitate cardiogenic shock and death.

Cardiac tamponade also causes an exaggerated respiratory variation in arterial blood pressure known as *pulsus paradoxus*. Inspiration normally lowers intrapericardial and right atrial pressures slightly, which enhances right heart filling and pulmonary blood flow. Left heart filling diminishes as more blood is held in the lungs and the inspiratory increase in right ventricular filling pushes the interventricular septum leftward. Thus left heart output and systemic arterial pressure normally decrease slightly during inspiration. Patients with pulsus paradoxus exhibit a fall in arterial pressure during inspiration of 10 mm Hg or more.[10,11]

43.4 CLINICAL PRESENTATION

Cardiac tamponade is relatively common in dogs, but rare in cats. Clinical findings reflect poor cardiac output and usually systemic venous congestion as well. The typical history includes exercise intolerance, abdominal enlargement, tachypnea, weakness, collapse or syncope, and sometimes cough. Collapse is more common in dogs with cardiac neoplasia than in those with idiopathic disease.[12] Nonspecific signs such as lethargy, inappetence, or other gastrointestinal maladies can develop before obvious ascites does.

43.4.1 Physical Findings

Jugular venous distention or a positive hepatojugular reflux,* hepatomegaly, ascites, labored respiration, and weakened femoral pulses are common physical findings.[3,12-15] Pulsus paradoxus is detected occasionally by femoral pulse palpation. High sympathetic tone commonly produces sinus tachycardia, pale mucous membranes, and prolonged capillary refill time. The precordial impulse is palpably weak with a large pericardial fluid volume, and heart sounds are muffled by moderate to large pericardial effusions.[2,12,13] In addition, lung sounds can be muffled ventrally with pleural effusion. Pericardial effusion alone does not cause a murmur, but concurrent cardiac disease may do so. Reduced lean body mass (cachexia) is apparent in some chronic cases.

Although right-sided congestion predominates, signs of biventricular failure can occur. Rapid pericardial fluid accumulation can cause acute tamponade, shock, and death without signs of pleural effusion, ascites, or radiographic cardiomegaly. Pulmonary edema, jugular venous distention, and hypotension may be evident in such cases.

* The hepatojugular reflux is assessed by applying firm pressure to the cranial abdomen while the animal stands quietly with head in a normal position. This pressure transiently increases venous return, but normally there is little to no change in jugular vein appearance. Jugular distention that persists while abdominal pressure is applied constitutes a positive (abnormal) test result.

43.5 DIAGNOSIS

Cardiac tamponade is often suspected from the history and physical examination, but thoracic radiographs and especially echocardiography are important for diagnosis. The electrocardiogram (ECG) may suggest pericardial disease in some cases. Laboratory findings reflect underlying disease or tamponade-induced prerenal azotemia or hepatic congestion, but are otherwise nonspecific (see Chapter 44, Pericardial Diseases, for further information about pericardial effusion diagnosis and differentiation of causes).

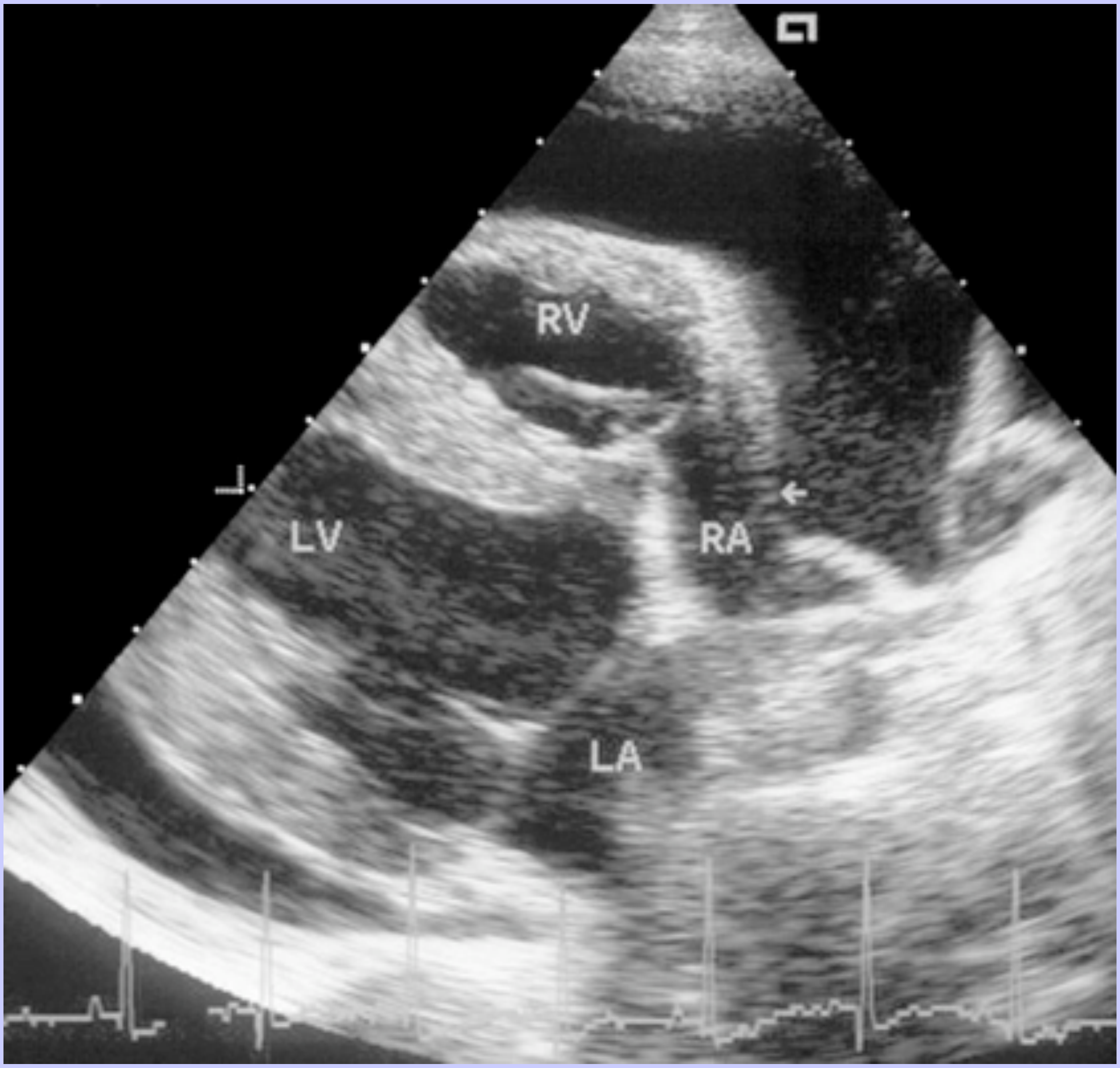
43.5.1 Thoracic Radiographs

The appearance of the cardiac silhouette depends on the volume of pericardial fluid as well as any underlying cardiomegaly.[2,3,16] Massive pericardial effusion causes the classic globoid-shaped cardiac shadow ("basketball heart") seen on both views. But other causes of a large, rounded heart shadow include dilated cardiomyopathy or marked tricuspid (with or without mitral) insufficiency. Smaller volumes of pericardial fluid allow some cardiac contours to be identified, especially those of the atria. Other radiographic findings associated with tamponade include pleural effusion, caudal vena cava distention, hepatomegaly, and ascites. Pulmonary infiltrates of edema or distended pulmonary veins are noted only occasionally. Tracheal deviation, a soft tissue mass effect, or metastatic lung lesions are seen in some cases of cardiac tamponade associated with heart base tumors.

43.5.2 Echocardiography

Because echocardiography is highly sensitive for detecting even small-volume pericardial effusion, it is the diagnostic test of choice.[2,3,17] The effusion appears as an echo-free space between the bright parietal pericardium and the epicardium. Abnormal cardiac wall motion and chamber shape, and intrapericardial or intracardiac mass lesions can also be visualized.[16-19] Cardiac tamponade is characterized by diastolic (and early systolic) compression or collapse of the right atrium and sometimes right ventricle (Figure 43-1).[18] The left ventricular lumen often appears small and the walls appear to be hypertrophied (pseudohypertrophy) because of the poor cardiac filling.

Figure 43-1 Right parasternal four-chamber echocardiographic image from a dog with cardiac tamponade. Pericardial fluid is seen surrounding the heart. Note the characteristic collapse of the right atrial wall *(arrow)* caused by elevated intrapericardial pressure. Electrocardiographic tracing along the bottom. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.



43.5.3

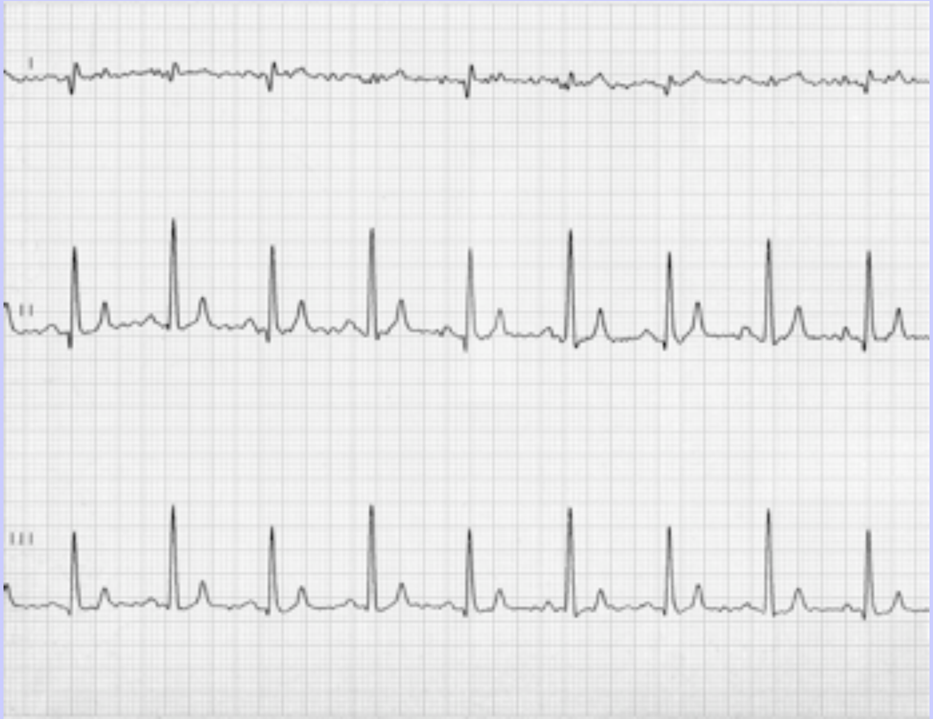
Electrocardiography

Although not specific for tamponade, ECG findings associated with large-volume pericardial effusion include reduced amplitude QRS complexes (less than 1 mV in dogs) and electrical alternans. The latter is a recurring, beat-to-beat alteration in the size or configuration of the QRS complex (and sometimes T wave) that results from the heart swinging back and forth within the pericardium (Figure 43-2).[20] Electrical alternans may be more evident at heart rates between 90 and 140 beats/min or in certain body positions (e.g., standing). ST segment elevation, suggesting an epicardial injury current, also is seen in some cases of pericardial effusion.[13,20] Sinus tachycardia is common with cardiac tamponade; atrial and ventricular tachyarrhythmias occur in some cases.

43.5.4 Central Venous Pressure

Central venous pressure (CVP) measurement may be useful in identifying tamponade, especially if it is difficult to assess jugular veins or it is unclear whether right heart filling pressure is elevated. CVP is normally in the range of 0 to 8 cm H_2O; CVP measurements of 10 to 12 cm H_2O are common with cardiac tamponade. Tamponade alters the CVP (and right atrial) waveform by markedly diminishing the *y* descent (during ventricular diastole). Although blood flow into the right atrium (and *x* descent on the CVP waveform) occurs during ventricular contraction, atrial filling is curtailed as the ventricles relax. Ventricular diastolic expansion causes an immediate rise in intrapericardial pressure when cardiac tamponade exists. The pericardial fluid instantly transmits this pressure to the atria, which severely impairs caval flow into the right atrium and prevents the normal early diastolic decrease in CVP (*y* descent). In contrast, a prominent *y* descent is associated with constrictive pericarditis.

Figure 43-2 Electrocardiogram showing sinus rhythm with electrical alternans, from a dog with large-volume pericardial effusion. Note the every-other-beat change in QRS complex size and configuration in each lead. See text for further information. Leads I, II, III: 50 mm/sec, 1 cm = 1 mV.



43.6 MANAGEMENT OF CARDIAC TAMPONADE

It is important to differentiate cardiac tamponade from other diseases that cause right-sided congestive signs because its management is unique. The compressed ventricles require high venous pressure to fill. By reducing cardiac filling pressure, diuretics and vasodilators further decrease cardiac output and exacerbate hypotension. Positive inotropic drugs do not improve cardiac output or ameliorate the signs of tamponade because the underlying pathophysiology is impaired cardiac filling, not poor contractility.

Immediate pericardiocentesis is indicated for cardiac tamponade. This sometimes also provides diagnostic information (see Chapter 44, Pericardial Diseases). Congestive signs should resolve after intrapericardial pressure is reduced by fluid removal. A modest dose of diuretic can be given after pericardiocentesis, but this is not essential. Subsequent management is guided by the underlying cause of the pericardial effusion and other clinical circumstances (see Chapter 44, Pericardial Diseases).

43.7 PERICARDIOCENTESIS TECHNIQUES

43.7.1 Preparation and Positioning

Pericardiocentesis is a relatively safe procedure when performed carefully. Depending on the clinical status and temperament of the animal, sedation may be helpful. ECG monitoring is recommended during the procedure; needle or catheter contact with the heart commonly induces ventricular arrhythmias. Although cardiac tamponade is uncommonly caused by coagulopathy, verifying that coagulation parameters are normal is helpful, if patient status allows time for this. Pericardiocentesis usually is performed from the right side of the chest. This minimizes the risk of trauma to the lung (via the cardiac notch) and major coronary vessels, most of which are located on the left. The patient usually is placed in left lateral recumbency to allow more stable restraint; sometimes sternal recumbency is used if the dog is cooperative. Alternatively, the author has had good success using an elevated echocardiography table with a large cut-out; the animal is placed in right lateral recumbency and the tap is performed from underneath (Color Plate 43-1). The advantage of this method is that gravity draws fluid down toward the collection site. But if adequate space is not available for wide sterile skin preparation or for needle or catheter manipulation, this approach is not advised. Echocardiographic guidance can be used, but is not necessary unless the effusion is of very small volume or appears compartmentalized. Sometimes pericardiocentesis can be performed successfully on the standing animal, but the risk of injury is increased if the patient moves suddenly.

Several methods can be used for pericardiocentesis. An over-the-needle catheter system (e.g., 16 to 18 gauge, 1.5 182 inch to 183 2 inches long) is recommended for most cases. Larger over-the-needle catheter systems (e.g., 12 to 14 gauge, 4 to 6 inches) allow for faster fluid removal in large dogs; a few extra small side holes can be cut (smoothly) near the tip of the catheter to facilitate flow, but care should be taken that the end of the catheter does not break off inside the patient. During initial catheter placement the extension tubing is attached to the needle stylet; after the catheter is advanced into the pericardial space and the needle removed, the extension tubing is attached directly to the catheter. In emergency situations or when an over-the-needle catheter is unavailable, an appropriately long hypodermic or spinal needle attached to extension tubing is adequate. A butterfly needle (18 to 21 gauge) is generally used in cats. For all methods a three-way stopcock is placed between the extension tubing and a collection syringe.

43.7.2 Pericardiocentesis Procedure

The skin is shaved and surgically prepared over the right precordium, from about the third to seventh intercostal spaces and from sternum to costochondral junction. Sterile gloves and aseptic technique should be used. The puncture site is identified by palpating for the cardiac impulse (usually between the fourth and sixth ribs just lateral to the sternum); the optimal site must be estimated if no precordial impulse is felt. Local anesthesia is recommended and is essential with use of a larger catheter. Two percent lidocaine is infiltrated (with sterile technique) at the skin puncture site underlying intercostal muscle and into the pleura. A small stab incision is made in the skin when using a larger catheter system.

The puncture site should be just cranial to a rib to avoid the intercostal vessels located caudal to each rib. Once the needle has penetrated the skin, an assistant should apply gentle negative pressure to the attached syringe (with three-way stopcock and extension tubing) as the operator slowly advances the needle toward the heart. In this way, any fluid will be detected as soon as it is encountered. Pleural fluid (usually straw colored) may enter the tubing first. It is helpful to aim the needle tip toward the patient's opposite shoulder. The pericardium causes increased resistance to needle advancement and may produce a subtle scratching sensation when contacted. The needle is advanced with gentle pressure through the pericardium; a loss of resistance may be noted with needle penetration, and pericardial fluid (usually dark red) will appear in the tubing. With a catheter system, the needle-catheter unit must be advanced far enough into the pericardial space that the catheter is not deflected by the pericardium as the needle stylet is removed. After the catheter is advanced into the pericardial space and the stylet removed, the extension tubing is attached to the catheter. Initial pericardial fluid samples are saved in sterile ethylenediaminetetraacetic acid (EDTA) and clot tubes for evaluation; then as much fluid as possible is drained.

A scratching or tapping sensation usually is felt if the needle or catheter contacts the heart; also, the device may move with the heartbeat, and ventricular premature complexes are often provoked. If this occurs the needle and catheter should be retracted slightly to avoid cardiac trauma. Care should be taken to minimize extraneous needle movement within the chest. If it is unclear whether pericardial fluid or intracardiac blood (from cardiac penetration) is being aspirated, a few drops can be placed on the table or into a clot tube and a sample spun in a hematocrit tube. Pericardial fluid does not clot (unless associated with very recent hemorrhage). The packed cell volume is usually lower than that of peripheral blood, and the supernatant appears yellow-tinged (xanthochromic). Furthermore, as pericardial fluid is drained, the patient's ECG complexes usually increase in amplitude, tachycardia diminishes, and the animal often breathes more deeply and appears more comfortable.

43.7.3 Complications of Pericardiocentesis

Ventricular premature beats occur commonly from direct myocardial injury or puncture. These are usually self-limited, resolving when the needle is withdrawn. Coronary artery laceration with myocardial infarction or further bleeding into the pericardial space can occur but is uncommon, especially when pericardiocentesis is done from the right side. Lung laceration causing pneumothorax or hemorrhage or both is also a potential complication during the procedure. In some cases, dissemination of infection or neoplastic cells into the pleural space may result.

43.8 SUGGESTED FURTHER READING*

MG Aronsohn, JL Carpenter: Surgical treatment of idiopathic pericardial effusion in the dog: 25 cases (1978-1993). *J Am Anim Hosp Assoc*. **35**, 1999, 521, *Results of surgical management and histopathologic examination in canine idiopathic pericardial effusion*.

RJ Berg: Pericardial effusion in the dog: a review of 42 cases. *J Am Anim Hosp Assoc*. **20**, 1984, 721, *Survey of clinical cases with pericardial effusion and cardiac tamponade*.

MW Miller, D Sisson: Pericardial disorders. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, St Louis, *General overview of pericardial diseases*.

* See the CD-ROM for a complete list of references.

44 Chapter 44 Pericardial Diseases

Nancy J Laste, DVM, DACVIM (Cardiology)

44.1 KEY POINTS

- The most common causes of pericardial effusion in dogs are hemangiosarcoma, idiopathic pericardial effusion, malignant mesothelioma (MM), and heart base tumors.
- Echocardiography is the main clinical tool for diagnosing pericardial effusion and cardiac masses.
- Dogs with a history of collapse have a shorter median survival time than dogs without collapse.
- Dogs with ascites have a longer median survival time than patients without ascites.
- MM can be difficult to differentiate from IPE, even with pericardial biopsy.
- Pericardial disease is more common in the dog than in the cat.
- The most common causes of pericardial effusion in the cat are lymphosarcoma, feline infectious peritonitis (FIP), and congestive heart failure.

44.2 INTRODUCTION

The clinical picture, pathophysiology, and therapeutic approach to acute pericardial effusion are covered in Chapter 43, Cardiac Tamponade and Pericardiocentesis. This chapter focuses on the differential diagnosis for canine and feline pericardial disease (Boxes 44-1 and 44-2) and details the more common causes of pericardial effusion in the dog.

44.3 CLINICAL SIGNS

The clinical signs associated with pericardial effusion will depend on the magnitude and rate of elevation of intrapericardial pressures. This will be determined chiefly by the volume of fluid within and the distensibility of the pericardial sac. Acute pericardial hemorrhage (hemangiosarcoma, left atrial tear) will typically result in signs of cardiac tamponade (see Chapter 43, Cardiac Tamponade and Pericardiocentesis) with lower volumes than those seen with causes associated with slower accumulation (idiopathic pericarditis, malignant mesothelioma [MM]). Accordingly, patients brought in for collapse have a worse long-term prognosis.[1] In addition, signs of right-sided congestive heart failure (jugular distention, ascites, pleural effusion) suggest a more chronic fluid accumulation, allowing time for cavitary fluid retention. Ascites has been correlated with a better long-term prognosis.[1] Disease processes associated with fibrosis of the pericardial sac will lead to clinical signs with lower volumes of effusion. In some cases (constrictive pericarditis) clinical signs are present even in the absence of pericardial effusion. Space-occupying lesions of the pericardial sac (pericardial cysts, peritoneopericardial diaphragmatic hernia) may result in right-sided congestive heart failure or cardiac tamponade, particularly with accompanying pericardial effusion.

44.3.1 Box 44-1 Pericardial Diseases in the Dog

44.3.1.1 Congenital Pericardial Disease

Pericardial cysts

Partial vs. total pericardial agenesis

Peritoneopericardial diaphragmatic hernia

44.3.1.2 Acquired Pericardial Disease and Pericardial Effusion

Transudative effusions

Hypoalbuminemia

Uremia

Congestive heart failure–associated

Exudative effusions

Septic pericarditis

Bacterial

Fungal (coccidiomycosis)

Protozoal (leishmaniasis)

Uremia

Hemorrhagic effusions

Coagulopathy

Heart base tumor*

Hemangiosarcoma*

Idiopathic pericardial effusion*

Left atrial rupture

Malignant mesothelioma*

Primary pericardial neoplasia (miscellaneous): metastatic, primary

Peritoneopericardial diaphragmatic hernia

Trauma

Uremia

44.4 SIGNALMENT

Golden Retriever dogs are significantly overrepresented for all major causes of pericardial effusion: hemangiosarcoma (HSA), idiopathic pericardial effusion (IPE), MM, and heart base tumor (HBT).[1–9] German Shepherd dogs are one of the breeds in which right atrial HSA and HBT are more common.[3,10–12] Boxers and other brachycephalic breeds traditionally are reported to be more predisposed to HBT, but in more recent reports Golden Retrievers and Labrador Retrievers were more commonly affected.[2,3,8,9] Saint Bernards and Labrador Retrievers are reported to be overrepresented for IPE, and Cocker Spaniel dogs and Labrador Retrievers may be overrepresented for MM (Laste, unpublished data).[2,8] Younger patients are at higher risk for congenital diseases (peritoneopericardial diaphragmatic hernia, pericardial cysts), and middle-aged to older patients are at higher risk for neoplastic causes.[3,13] Male dogs are more likely to develop IPE per most reports.[1,2,6,8,10] There is no reported 184 sex predilection with neoplastic causes of pericardial effusion, but intact animals, particularly intact females, have a 185 significantly lower incidence of cardiac tumors.[3]

44.4.1 Box 44-2 Pericardial Diseases in the Cat

44.4.1.1 Congenital Pericardial Disease

Peritoneopericardial diaphragmatic hernia*

44.4.1.2 Acquired Pericardial Disease

Congestive heart failure*

Feline infectious peritonitis*

Hypoalbuminemia

Idiopathic

Lymphosarcoma*

*More common causes.

44.5 HISTORY

The history may help determine the likelihood of acute hemorrhage (hemorrhage from a tumor) versus a more chronic accumulation of pericardial effusion more typically associated with the insidious disease processes (IPE, MM). Travel history, history of trauma, or possible rodenticide exposure may be important in forming the differential diagnosis list for each patient. A history of preexisting valvular disease will raise the index of suspicion for the possibility of left atrial rupture with acute hemopericardium. In addition, previously diagnosed pericardial disease and the chronicity of the effusion may make some diagnoses more likely than others. Patients surviving longer than 7 months are unlikely to have HSA.[1] The longer the survival, the more likely it is that IPE is present.

44.6 DIAGNOSTIC FINDINGS

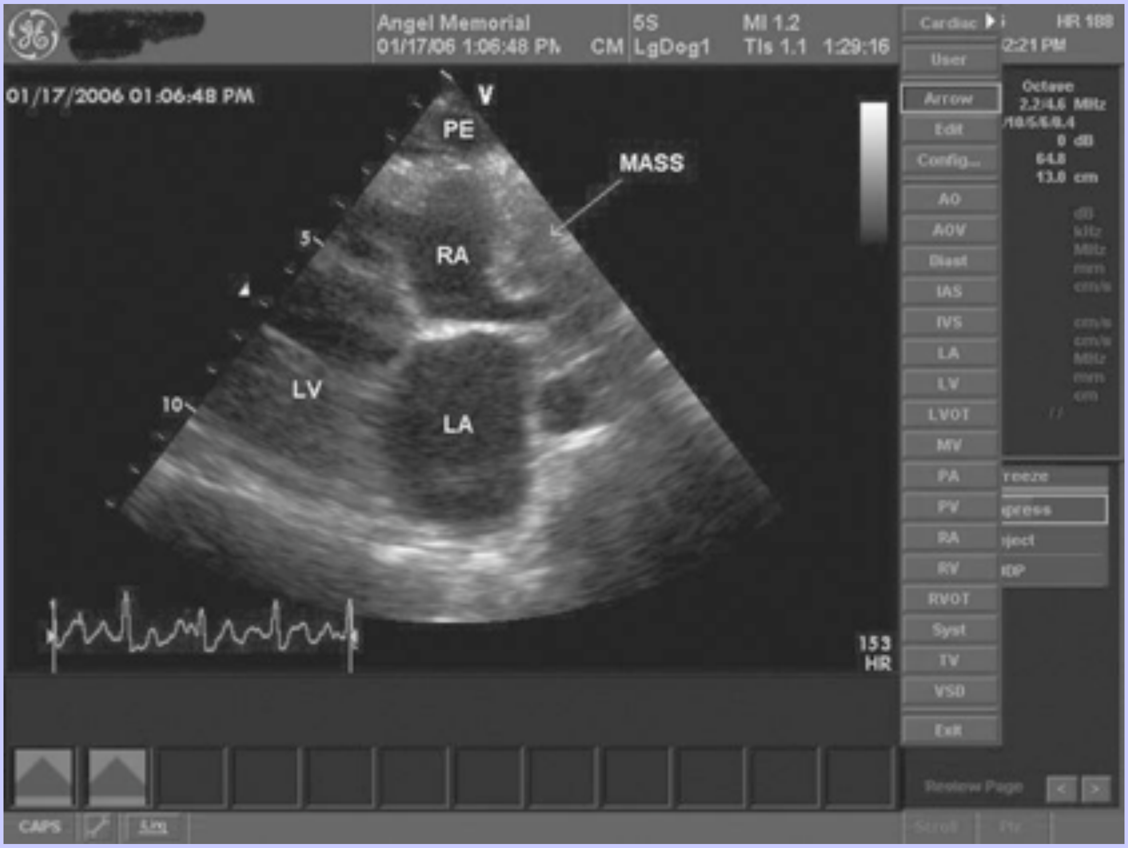
44.6.1 Laboratory Findings

Laboratory findings are not specific for most cases of pericardial effusion aside from marked azotemia in patients with uremic pericarditis. Increases in circulating nucleated red blood cells have been reported in patients with right atrial HSA, but this has not been substantiated by other sources.[10] Anemia may be noted in the patient with pericardial effusion, regardless of the underlying cause, but this has not been reported consistently.[2,10]

44.6.2 Radiographic Findings

Radiographic findings are variable. Heart size may be remarkably normal in patients with acute hemopericardium. The caudal vena cava usually is distended, suggesting elevated right atrial pressures. In cases of chronic-accumulation pericardial effusion, the heart may have the globoid “basketball” appearance classically described. Mass lesions may be suggested by bulges at the heart base. Pulmonary metastases may be noted in some cases with cardiac neoplasia. With more chronic disease, pleural effusion may be present and may obscure the cardiac silhouette and pulmonary parenchyma. Patients with peritoneopericardial diaphragmatic hernia (PPDH) show confluence of the cardiac silhouette and the diaphragm and, depending on the extent of organ involvement, the abdominal cavity may appear devoid of abdominal contents. If there are gastrointestinal segments within the pericardial sac, there may be a suggestive gas pattern, but omental fat and liver are more typically herniated through the defect. Sternal defects may be noted and, if present, are suggestive of a PPDH. Metallic foreign bodies are an uncommonly reported cause of pericardial effusion and can be noted on thoracic radiographs.[14]

Figure 44-1 Right parasternal long-axis 3-dimensional echocardiographic picture showing a right atrial mass (hemangiosarcoma, presumptive) and associated pericardial effusion in a dog. *LA,* Left atrium; *LV,* left ventricle; *PE,* pericardial effusion; *RA,* right atrium.



44.6.3 Electrocardiographic Findings

Low-amplitude QRS complexes are the most consistently reported electrocardiographic finding.[2,4,10] Although electrical alternans (beat-to-beat variations in the R wave amplitude) is described as a classic finding with pericardial effusion, this is reported only 6% to 37% of the time.[2,10] Electrical alternans is associated with higher volumes of pericardial effusion and is thought to be related to the heart swinging within the fluid-filled pericardial sac. ST segment changes, and ventricular or supraventricular arrhythmias may be present in patients with cardiac tamponade.[2,4,7,9]

44.6.4 Echocardiographic Findings

Two-dimensional echocardiography is the main diagnostic tool for pericardial disease.[15] It can be used to confirm the presence of pericardial effusion, roughly quantitate the amount, and identify whether signs of cardiac tamponade exist (Figure 44-1). Careful survey of the right atrium (particularly the right auricle), heart base, and main pulmonary artery is made because the vast majority of mass lesions associated with pericardial effusion are found in these areas (Figures 44-2 and 44-3). HBT generally can be identified adjacent to the aorta on the standard transthoracic views but HSA, particularly associated with the right auricular appendage, may be difficult to see. Therefore the absence of a mass lesion on echocardiography does not rule out the possibility of HSA or other neoplasia. Overall, echocardiography has been estimated to be up to 90% sensitive for the detection of cardiac masses.[16] The heart base and right auricle are surveyed more easily using transesophageal echocardiography, but this technique requires specialized equipment as well as general anesthesia and is thus limited in its practical application. False-positive findings (noting a mass when one is not present) have been reported. Normal cardiac structures can mimic a mass when imaged in oblique positions, particularly to the novice sonographer. One should use care not to overinterpret brightly echogenic periaortic fat. The myocardial texture should also be observed for any changes that could suggest primary or metastatic myocardial neoplasia (LSA, other). In patients that have suffered an endocardial split and left atrial tear, the preexisting valvular disease is noted (mitral valve thickening, varying degrees of left atrial and ventricular dilation), as well as the presence of pericardial effusion and a laminated clot within the pericardial sac, conforming to the heart.[16] Color-flow Doppler allows the identification of a jet aimed at the left atrial free wall, and occasionally an intraatrial clot may be seen adhering to the site of perforation.

Figure 44-2 Right parasternal short-axis 2-dimensional echocardiographic picture of the same patient in Figure 44-1. *PE,* Pericardial effusion; *RA,* right atrium.

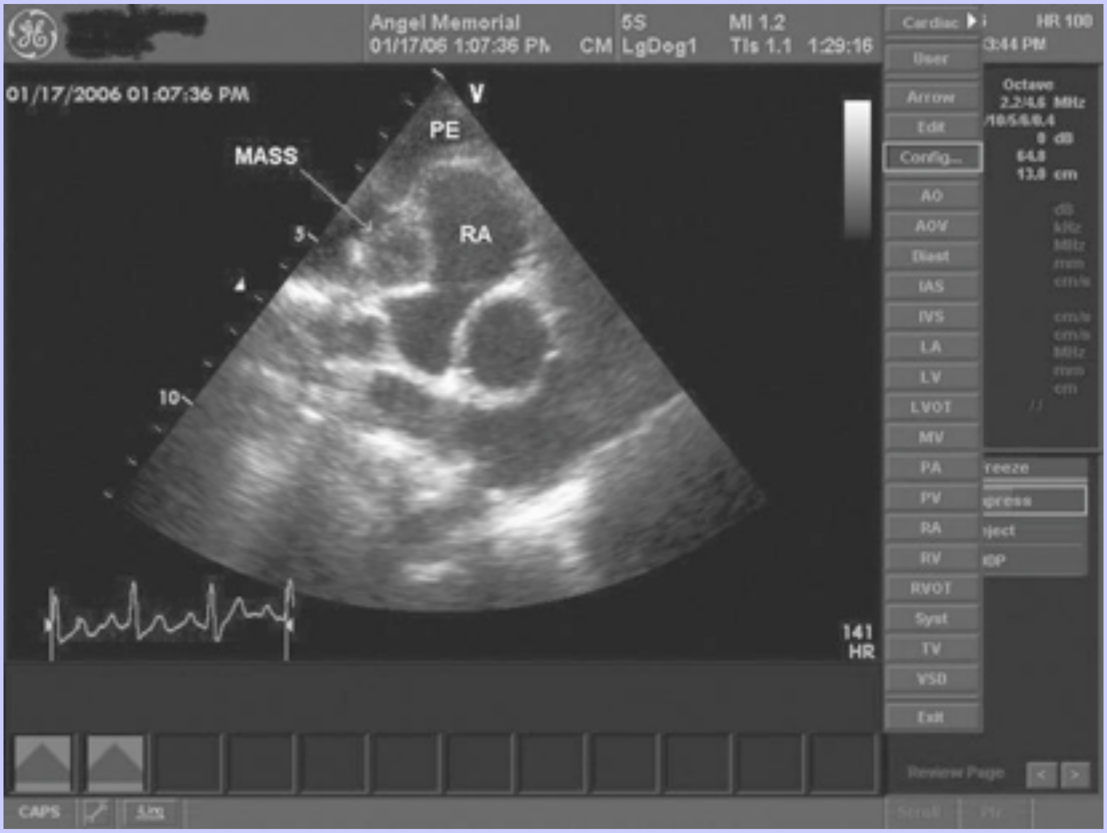
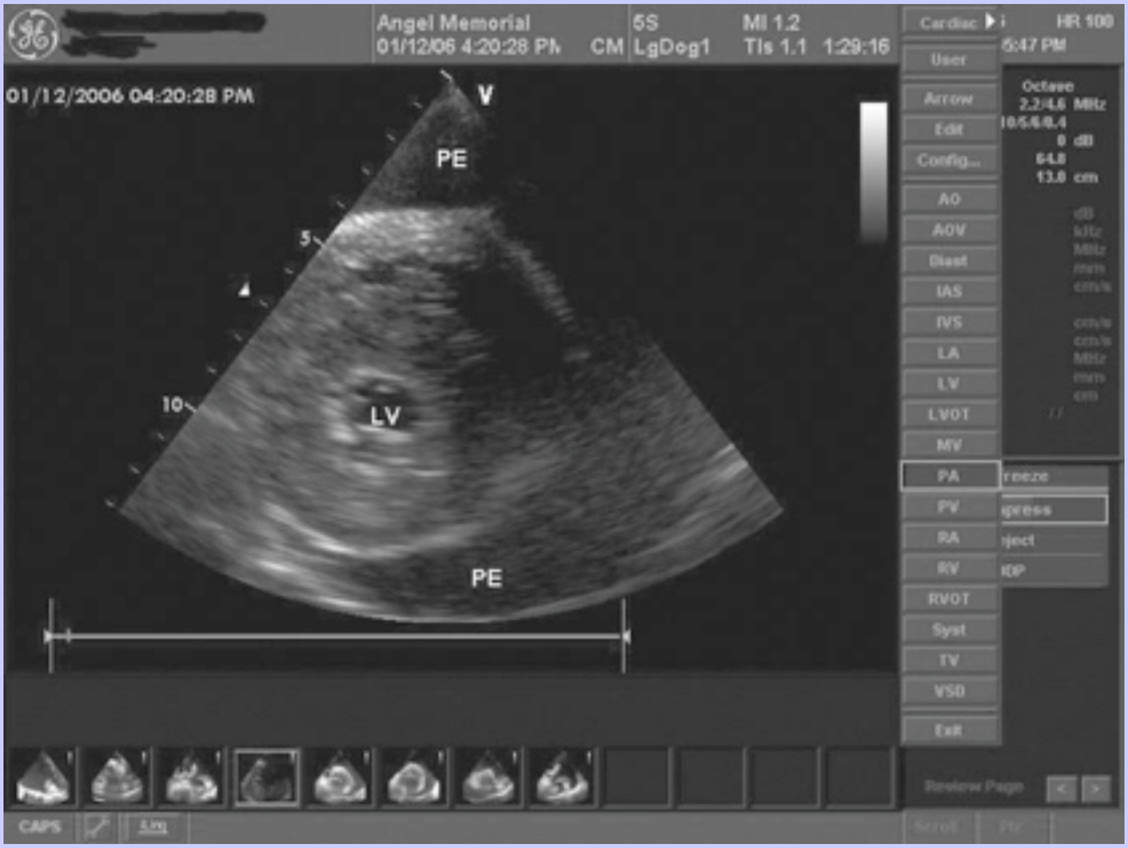


Figure 44-3 Right parasternal short-axis two-dimensional echocardiographic picture of a dog with a very large pericardial effusion. *LV,* Left ventricle; *PE,* pericardial effusion.



44.6.5 Pericardial Fluid Analysis

Pericardiocentesis generally is indicated for hemodynamic stabilization of the patient and the fluid is submitted for cytologic analysis. Pericardial effusion is grossly hemorrhagic in most cases. The fluid should always be submitted for cytologic analysis, because occasionally it will be diagnostic for causes requiring specific therapy (LSA, FIP, septic pericarditis).[16-19] In most cases, however, fluid analysis is not diagnostic.[20] MM may be suspected from pericardial fluid, but neoplastic cells may be difficult or impossible to differentiate from reactive mesothelial cells. Most pathologists will not make a diagnosis of MM without a tissue biopsy. There have been several investigations attempting to find qualities of pericardial fluid (pH, lactate, glucose) that will differentiate benign versus malignant origins. Although early investigation showed some promise, subsequent studies have found too much overlap between the two groups to make this an effective clinical tool.[21–23]

44.6.6 Advanced Imaging Modalities

Computed tomography and magnetic resonance imaging are excellent for identifying cardiac-associated masses in human patients, but these diagnostic tools are rarely used for veterinary patients because they are available only at larger referral centers, are relatively expensive, and require general anesthesia.

44.6.7 Surgical Exploration

44.6.7.1 Thoracoscopy

Thoracoscopy can be used to facilitate minimally invasive exploration of the thorax, to allow pericardial biopsy, and to create a pericardial window to prevent recurrent pericardial effusion.[24] This technique generally is used for patients that have recurrent pericardial effusion in the absence of a mass lesion. However, it may also be used as a palliative measure for patients with an HBT or right atrial tumor (HSA, presumptive) to avoid recurrent hospitalization for cardiac tamponade. Pleural and pulmonary surfaces can be inspected for metastatic disease and biopsies obtained. In cases with confirmed or suspected diffuse neoplasia (MM), the disease can be staged (microscopic versus gross disease) to help establish prognosis. Thoracostomy tubes can be placed concomitantly to facilitate intracavitary chemotherapy.

Dorsal recumbency is the easiest position for creating a pericardial window but limits exploration of the heart base. In cases where more complete exploration is desired, the patient may be positioned in lateral recumbency and multiple ports placed to allow better access to the heart base. Biopsy of associated mass lesions (right auricular mass, HBT) may be performed, but the risk of poorly controlled hemorrhage after biopsy of these very vascular tumors should be discussed with the owner. Full coagulation profiles should be run on all patients before thoracoscopy and any identified coagulopathies addressed with fresh frozen plasma transfusion before the procedure. Tumor biopsies are avoided in patients with coagulopathies and the surgical procedure limited to the palliative pericardial window.

44.6.7.2 Exploratory Thoracotomy

Exploratory thoracotomy allows the definitive detection of any cardiac-associated masses and provides pericardial tissue for histopathologic analysis. If possible, masses are resected; if resection is not possible, biopsy can be obtained. A subtotal pericardectomy is recommended at the time of the procedure to avoid recurrent cardiac tamponade. The main disadvantage of thoracotomy is patient morbidity. If the disease is advanced (pulmonary metastasis, large nonresectable mass compressing the heart), nonrecovery (euthanasia) should be considered. This possibility should be discussed with the owner before surgery.

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44.7 THERAPEUTIC PLANS AND PROGNOSIS

The reported causes of pericardial disease in the dog are noted in Box 44-1. With many of the causes (hypoalbuminemia, uremia, right-sided congestive heart failure) the amount of pericardial effusion is smaller and does not typically result in significant cardiac compromise. The more common causes of pericardial effusion in the dog will be discussed in more detail later in this chapter.

Acute management of pericardial effusion is mainly pericardiocentesis (see Chapter 43, Cardiac Tamponade and Pericardiocentesis). Following pericardiocentesis, the patient should be monitored for recurrent pericardial bleeding, which is highly suggestive of an intrapericardial mass lesion. The long-term management plan for pericardial disease depends upon the underlying cause. After the diagnostic evaluation has been completed, patients can be classified tentatively as having no mass noted on echocardiography (echo-negative), a mass associated with the right atrium or right auricle (HSA presumptive), HBT, or more specific causes (PPDH, left atrial tear). Generally, echo-negative dogs are approached conservatively (discharged and monitored for recurrent pericardial effusion).

If the pericardial effusion does recur, the timing and pattern of recurrence may be suggestive as to the underlying cause. Patients returning in days to weeks with apparently abrupt recurrence are suspected to have an occult HSA, which may be detected on a repeat echocardiographic study. Right auricular HSA is best visualized when pericardial effusion is present and, when possible, the study should be performed before doing pericardiocentesis. In patients with less aggressive underlying disease processes, pericardial effusion may not recur (IPE) or may not recur for months to years (IPE, MM). Patients with an identified mass lesion have a variety of options as discussed later in this chapter.

44.7.1 Less Frequent Causes of Pericardial Disease

Animals with transudative effusion do not generally require treatment beyond medical management of the underlying disease process. Those with bacterial, fungal, or protozoal pericarditis require surgical management coupled with medical therapy directed at the underlying pathogen.[25–28] Patients with a PPDH who are symptomatic for that defect also require surgery. This defect is sometimes diagnosed as an incidental finding, in which case elective surgery should still be discussed.

Left atrial tears may be identified by echocardiography. These patients may be stable enough to treat conservatively with management of associated congestive heart failure (CHF) and the underlying heart disease, but they are at high risk for recurrent pericardial bleeding. Pericardiocentesis generally is avoided when possible because changes in the intrapericardial pressure may actually disrupt thrombosis and promote further hemorrhage. Surgical attempts to repair left atrial tears have been described. However, these procedures may be difficult to justify with advanced cardiac disease unless mitral valve repair or replacement will also be performed.

44.7.2 Heart Base Tumors

HBTs may be used as a catch-all term for masses that are seen in this location, but HBTs do not appear to be associated directly with the right atrium or other cardiac chambers. Alternatively, it may be used more specifically to indicate aortic body tumors (ABTs), chemodectomas that arise adjacent to the aortic root. Malignant transformation of ectopic thyroid and parathyroid tissue has also been reported in this location, so diagnosis requires biopsy and histopathology.[15]

Patients with HBT may be treated conservatively using periodic echocardiography to evaluate for recurrent effusion. A more aggressive approach includes thoracotomy to evaluate the mass for resectability, or biopsy for nonresectable lesions. A subtotal pericardectomy is performed to allow persistent effusion to drain into the pleural space, thereby avoiding future cardiac tamponade and pericardiocentesis. In more recent years a thoracoscopic pericardial window has emerged as a less-invasive palliative option. Although biopsy is feasible using this method, differentiation of the mass from nearby great vessels can be difficult and hemostasis may be more difficult.

The prognosis for HBT is variable. The classic description is one of a slow-growing tumor (ABT). HSA can appear to be a heart base mass but is expected to grow and metastasize much more quickly than an ABT. Some heart base masses can be associated with aggressive atrial or ventricular arrhythmias; others may cause signs of collapse related to poor cardiac output caused by impingement on the atria and great vessels. Signs of CHF may also be present. Ehrhart and colleagues reported survival times in 24 dogs with ABT as longer (median 730 days, range 1 to 1621 days) in patients that had a pericardectomy than in those that did not (median 42 days, range 1 to 180 days).[9] Of 46 dogs with a description of HBT that had histologic confirmation of the tumor type, only 24 were confirmed to have ABT. HSA was diagnosed in 16, 3 had ectopic thyroid carcinoma, and 3 had MM. Thus the echocardiographic diagnosis of heart base mass is not specific for ABT. Of the 24 dogs with ABT, 5 were Golden Retrievers, 5 were Labrador Retrievers, and 2 were German Shepherds. Only two dogs were brachycephalic (1 Boxer and 1 Boston Terrier).

44.7.3 Hemangiosarcoma

HSA is the most common primary cardiac tumor in the dog and typically is associated with the right atrial body, right atrioventricular junction, or the right auricular appendage.[3,11] HSA is an aggressive tumor with pulmonary metastasis presumed to be present at the time of diagnosis.[7] Approaches to therapy include euthanasia after the mass is identified, stabilization by pericardiocentesis followed by home care until symptoms of tamponade recur, palliative pericardial window via thoracoscopy, thoracotomy for pericardectomy, and possible tumor resection with or without chemotherapy. Right auricular masses that do not infiltrate the right atrial body may be removed along with the auricle using stapling equipment. Although early reports suggest a high incidence of complications and poor survival, more recent reports suggest that the prognosis may be better than previously reported.[7,29] Further study is required to better evaluate the effects of combined pericardectomy and chemotherapy with or without mass resection on the long-term prognosis for dogs with HSA.

44.7.4 Idiopathic Pericardial effusion

Idiopathic pericardial effusion (IPE) describes the syndrome of pericardial effusion, often recurrent, in the absence of known underlying cause. IPE is also known as idiopathic hemorrhagic pericardial effusion, benign idiopathic pericardial effusion, benign fibrosing pericarditis, and idiopathic pericardial hemorrhage. Biopsy 187 reveals inflammation and 188 varying degrees of fibrosis without evidence of neoplasia.[6,30] Although this syndrome appears to be a common cause of pericardial effusion in the dog, there is substantial overlap with cases of MM, which can also have a slow and insidious progression. In addition, small heart base masses or auricular appendage masses missed on echocardiography may lead erroneously to a working diagnosis of IPE.

44.7.4.1 Constrictive Pericarditis

Constrictive (restrictive) pericarditis is a subtype of idiopathic pericarditis. Fibrosis renders the pericardial sac nondistensible, so that cardiac tamponade occurs with small amounts of effusion (effusive-constrictive pericarditis) or even without pericardial effusion (pure constrictive pericarditis).[30] Restrictive physiology has been reported in association with tumor infiltrate, infectious pericarditis, and with pericardial foreign bodies.[26,27,31] Effusive-constrictive pericarditis most frequently develops in patients with a chronic history of pericardial effusion, with decreasing volumes of effusion present on serial examinations and centeses. Patients with constrictive pericarditis typically have signs of right-sided CHF (ascites, pleural effusion, jugular distention) without any underlying cardiac disease. Thoracotomy and pericardectomy should be recommended for patients with effusive-constrictive disease, although owners of older dogs may elect to start with a thorascopic pericardial window. In the latter case, owners are warned that the CHF may persist or recur if the remaining pericardium continues to fibrose around the heart.

Constrictive pericarditis is difficult to diagnose in the absence of pericardial effusion. Cardiac catheterization provides characteristic data but requires specialized equipment and is expensive. In patients for which there is a strong clinical suspicion of constrictive pericarditis, the patient may be referred for thoracotomy. Another option is exploratory thoracoscopy (where available) in which manipulation of the pericardial sac (thick and difficult to cut) confirms the suspicion. The procedure can be converted to an open chest thoracotomy for pericardectomy to allow complete release of the heart from the pericardial sac. Varying degrees of epicarditis generally accompany constrictive pericarditis. Although surgical “epicardial stripping” has been recommended for this condition, questions remain about the safety, efficacy, and necessity of this technique.[32]

44.7.5 Malignant Mesothelioma

MM does not appear to be as rare as was suggested previously in the literature and may be the underlying cause for some cases initially identified as IPE. Golden Retriever dogs are greatly overrepresented for this disease.[4,5] MM develops from the malignant transformation of the mesothelial cells lining the pericardial sac, pleural space, and occasionally the peritoneal space. MM may be suspected from pericardial or pleural fluid samples by a pathologist experienced with this disease, but definitive diagnosis requires histopathologic confirmation from tissue obtained via thoracoscopy or surgery.

MM is diagnosed frequently in patients that have a history of chronic and recurrent pericardial effusion, and that develop hemorrhagic pleural effusion following a pericardectomy. This suggests that MM may be insidious and difficult to diagnose, or alternatively that chronic inflammation may predispose dogs to the later development of MM.[5,13] In Stepien's small case series of 17 dogs with pericardial effusion, 2 of 8 dogs eventually diagnosed with MM were originally classified as having IPE via biopsy.[33] In this series of dogs, the chance of developing hemorrhagic pleural effusion was greatest during the first 3 months postoperatively.

The prognosis for dogs with MM is variable. Some animals may respond temporarily (months) to complete fluid drainage with a chest tube followed by prednisone at antiinflammatory dosages, with no recurrence of effusion for up to 6 months. Intracavitary cisplatin therapy has been described for the management of pleural and pericardial mesothelioma.[34] The author has found this therapy to be ineffective in dogs that have malignant pleural effusion and grossly evident pleural disease. Intracavitary and intravenous chemotherapy may be more successful in delaying metastasis in patients with a grossly normal thorax, no pleural effusion, and histopathologic confirmation of pericardial MM.[35]

44.8 PERICARDIAL DISEASE IN THE CAT

Pericardial disease is not nearly as common in the feline as the canine patient.[16] The reported causes of pericardial disease in the cat are listed in Box 44-2. Of these, FIP, LSA, and heart failure are the most common.[36] IPE has not been reported in cats. However, the author has treated a 4-year-old neutered male cat with a large volume of transudative pericardial effusion, no apparent underlying cause, and no fluid recurrence at 18 months postpericardiocentesis. PPDH occurs more commonly in the feline than in the canine patient. Many of these are incidental radiographic findings (even in the older patient), or the patient may become symptomatic when vascular compromise to an incorporated organ (usually omentum or a liver lobe) leads to fluid production and signs of cardiac tamponade. Surgical repair of the defect and removal of devitalized tissue are indicated.

44.9 SUGGESTED FURTHER READING*

AM de Laforcade, LM Freeman, EA Rozanski, JE Rush: Biochemical analysis of pericardial fluid and whole blood in dogs with pericardial effusion. *J Vet Intern Med*. **19**, 2005, 833, *This scientific article looks further into the use of various biochemical param-eters of pericardial fluid (pH, lactate) to try to accurately predict the etiology of canine pericardial disease*.

JE Rush, BW Keene, PR Fox: Pericardial disease in the cat: a retrospective evaluation of 66 cases. *J Am Anim Hosp Assoc*. **26**, 1990, 39, *This is the most extensive case series of feline pericardial disease published to date*.

CS Sims, AH Tobias, DW Hayden, et al.: Pericardial effusion due to primary cardiac lymphosarcoma in a dog. *J Vet Intern Med*. **17**, 2003, 923, *This is a case description of a dog presenting with cardiac lymphosarcoma*.

RL Stepian, NT Whitley, RR Dubielzig: Idiopathic or mesothelioma-related pericardial effusion: clinical findings and survival in 17 dogs studied retrospectively. *J Small Anim Pract*. **41**, 2000, 342, *This retrospective study provides a good description of the different causes of pericardial effusion and highlights some of the difficulties surrounding antemortem diagnosis of canine pericardial disease*.

WA Ware, DL Hopper: Cardiac tumors in dogs: 1982–1995. *J Vet Intern Med*. **13**, 1999, 95.

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* See the CD-ROM for a complete list of references.

45 Chapter 45 Bradyarrhythmias and Conduction Abnormalities

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45.1 KEY POINTS

- Disease of cardiac tissue can result in regions of conduction delay or conduction block.
- Conduction delays or blocks can result in bradyarrhythmias or tachyarrhythmias.
- Conduction abnormalities that lead to bradyarrhythmias are due to conduction delays or conduction blocks within the specialized conduction system.
- Dogs and cats with persistent bradyarrhythmias causing clinical signs such as syncope generally require implantation of an artificial pacemaker.
- Right bundle branch block by itself does not usually cause clinical sequelae.
- Left bundle branch block usually indicates widespread disease and almost never occurs by itself as a benign abnormality.

45.2 INTRODUCTION

Conduction abnormalities may or may not produce an arrhythmia. The term *arrhythmia* literally means “no rhythm”. Because of this, some prefer the term *dysrhythmia*. However, arrhythmia is the more commonly used term and is used here to describe any abnormal heart rhythm. Mechanisms of arrhythmias primarily include disorders of cardiac electrical impulse conduction and electrical impulse formation. Conduction abnormalities commonly result in conduction delays and blocks but can also contribute to formation of ectopic tachyarrhythmias (premature depolarizations) by producing a substrate for reentry. Abnormalities of impulse formation produce both bradyarrhythmias and tachyarrhythmias.[1]

45.3 DISORDERS OF ELECTRICAL IMPULSE CONDUCTION

Almost all cardiac tissues depolarize during systole and help conduct the depolarization wave from site to site. Disease of cardiac tissue can result in regions of conduction delay or conduction block. Conduction delays or blocks can result in bradyarrhythmias or tachyarrhythmias.[1]

45.4 CONDUCTION ABNORMALITIES LEADING TO BRADYARRHYTHMIAS

Conduction abnormalities that lead to bradyarrhythmias are due to conduction delays or conduction blocks within the specialized conduction system. Conduction starts in the tissues surrounding the sinus node and terminates in the Purkinje network in the ventricles. Slowed conduction from the sinus node to the internodal tracts (first-degree sinoatrial block) does not cause any perceptible abnormality on an electrocardiogram (ECG) because it occurs before the P wave is inscribed. An intermittent conduction block in this region (second-degree sinoatrial block) results in the heart rhythm stopping, usually only for one beat, because of the lack of a P-QRS-T complex on the ECG. Complete blockage of conduction from the sinus node to the internodal tracts and atria theoretically results in atrial standstill and forces the atrioventricular (AV) node to take over the pacing function of the heart at a slower rate. In reality, other regions of automaticity (e.g., tissue around the coronary sinus) in the atria probably take over the function of the sinus node in this situation.[1]

Slowed conduction through the AV conduction system results in a prolongation in the PR interval (first-degree AV block). This conduction delay can occur in the proximal AV bundle, the AV node, the bundle of His, or the bundle branches (if both the left and right bundle branches are affected). It theoretically may also occur in the internodal tracts. An intermittent complete block of conduction results in the intermittent loss of a QRS-T complex (second-degree AV block). Third-degree AV block occurs when conduction is completely blocked through the AV node, bundle of His, or both bundle branches. Complete block of conduction through the internodal tracts is also reported to produce complete AV block (third-degree AV block) in dogs.[2]

45.5 DISORDERS OF IMPULSE FORMATION

Disorders of impulse formation encompass enhanced or depressed impulse formation by abnormal pacemaker cells and abnormal impulse formation by cells that are not normally automatic.[1]

45.6 DEPRESSED NORMAL AUTOMATICITY

A depression in normal automaticity results in a decrease in the discharge rate of an automatic site. This can be due to disease of the automatic tissue or depression of automatic tissue as a result of diverse influences, such as the parasympathetic nervous system, electrolyte disturbances (e.g., hyperkalemia), endocrine abnormalities (e.g., hypothyroidism), and hypothermia. To be manifested as a bradyarrhythmia, the sinus node must be affected, either 189 190 by itself or in combination with subsidiary pacemaker sites. For example, if the automatic cells within the AV node are suppressed by stimulation of the left vagus nerve such that their inherent rate decreases from 50 to 30 beats/min, but the sinus node continues to depolarize at a rate of 100 beats/min, the AV nodal cell depression will never be identified because the faster sinus nodal rate continues to control the heart rate. Normal automaticity can also be depressed by disease. Sick sinus syndrome is a disease in which the sinus node tissue is diseased and destroyed. When most of the sinus node tissue is destroyed, it loses its ability to produce depolarizations automatically.[1]

45.7 SPECIFIC BRADYARRHYTHMIAS

45.7.1 Sinus Bradycardia

Sinus bradycardia is a regular rhythm that originates in the sinus node but at a rate that is too slow for a given situation. A sinus rate less than 60 beats/min in an awake dog in an examination room is generally considered too slow. However, the sinus rate can be as slow as 20 beats/min in a normal dog that is sleeping. A heart rate less than 100 to 120 beats/min in a cat is generally too slow, although it may produce no clinical signs. Sinus bradycardia is an uncommon rhythm disturbance in clinical veterinary practice. It is identified most commonly during an anesthetic overdose. Other causes include increased vagal tone (athletic training, increased intracranial pressure, severe gastrointestinal (GI) or respiratory disease), sick sinus syndrome, hypothermia, severe hypothyroidism, and administration of parasympathomimetic or sympatholytic drugs, such as xylazine, digoxin, and β-blockers. Sick sinus syndrome is discussed later in this chapter. [1,3]

45.7.1.1 Treatment

Treatment of sinus bradycardia is unnecessary unless clinical signs are evident, and it depends on the underlying cause. If drug administration is precipitating the problem, it should be discontinued. If the problem is peracute, such as in a patient under anesthesia, atropine should be administered in an attempt to increase the heart rate. If this is unsuccessful, a β-adrenergic agonist, such as isoproterenol, can be administered; however, close monitoring for hypotension is recommended. Conscious patients that have no apparent underlying cause should be given atropine (0.04 mg/kg SC or IV) and an ECG repeated 30 minutes or 10 minutes later, respectively. In a dog with a normal sinus node, the heart rate should increase to 140 to 200 beats/min. If a normal response is identified, the diagnosis of increased vagal tone is made. If the dog is symptomatic, chronic anticholinergic therapy can be initiated. If there is no response or if the response is only partial (heart rate increases to 70 to 130 beats/min), sick sinus syndrome is most likely present.[1]

45.7.2 Sinoatrial Block

Sinoatrial block occurs when the tissue surrounding the sinus node fails to conduct the depolarization to the atria and ventricles. Some, but not all, depolarizations are conducted in a second-degree sinoatrial block. This is the most commonly diagnosed type of sinoatrial block. Second-degree sinoatrial block is diagnosed on an ECG when a pause occurs after a sinus beat and the interval between beats is an exact multiple (e.g., 2 or 3 times) of the normal P-P interval. This indicates that the sinus node is most likely depolarizing at its normal rate, but the depolarization is being blocked intermittently from conducting to the atria and internodal tracts. Consequently, no P waves and no QRS-T complexes are produced.[1]

45.7.3 Sinus Arrest

Sinus arrest is a cessation of sinus node activity for a short period. Although sinus arrest commonly is described as a pause in the sinus rhythm that lasts for more than two normal R-R intervals, this can also be seen with severe sinus arrhythmia. Consequently, there is a “gray zone” between severe sinus arrhythmia and sinus arrest in the dog.[1] Sinus arrest in dogs most commonly is due to either sinus node dysfunction or increased vagal tone. Sinus node dysfunction usually is due to end-stage sinus node disease and is commonly called *sick sinus syndrome*. Sinus node dysfunction in dogs can produce other arrhythmias, including sinus bradycardia and the so-called *tachycardia-bradycardia syndrome*. A supraventricular tachycardia can sometimes be seen with sick sinus syndrome, presumably because of reentry in or around the diseased sinus node. However, sinus arrest is the most common manifestation of end-stage sinus node disease in dogs.[4] Increased vagal tone can also produce periods of sinus arrest and can, on occasion, produce pauses long enough to cause syncope. Vagal tone can be increased secondary to chronic respiratory disease or secondary to systemic disease (e.g., GI disease).[1]

45.7.4 Escape Beats

Sinus arrest can last for a short period (<1 second in a dog) and be terminated by the sinus node depolarizing again. Sinus arrest can also last long enough that a subsidiary pacemaker, such as the AV node, takes over the heart rhythm. When the AV junction or the Purkinje fibers take over the heart rhythm, QRS complexes occur after a pause or occur at a rate between 20 and 60 beats/min. Depolarizations that occur after a pause are called *escape beats,* and the slow rhythms are called *escape rhythms*. Escape beats normally originate either from the

AV junctional region or from Purkinje fibers. Because the rates for these two sites differ, one can determine the origin of an escape beat by determining the rate at which it fires.

45.7.5 Sick Sinus Syndrome

Dogs with diffuse conduction system disease or with increased vagal tone to both the sinus node and the AV node may have more prolonged periods of sinus arrest because the subsidiary pacemakers are either suppressed or dysfunctional. If a period of sinus arrest lasts for more than approximately 6 seconds, weakness and syncope will occur.[4]

45.7.5.1 Treatment

Dogs with sick sinus syndrome generally require the implantation of an artificial pacemaker to prevent syncope. Occasionally a dog that is partially responsive to atropine administration can be treated chronically with an anticholinergic or a sympathomimetic agent. However, the disease usually progresses to the point that the arrhythmia becomes unresponsive to drug therapy and pacemaker implantation is required.

Dogs with vagally induced sinus arrest require therapy if clinical signs of episodic weakness or syncope occur. Anticholinergic or sympathomimetic therapy should be tried initially. Anticholinergic agents that can be administered on a long-term oral basis include atropine, isopropamide, prochlorperazine plus isopropamide (Darbazine), and propantheline. Atropine tablets are no longer manufactured. Isopropamide and propantheline are weak anticholinergic agents compared with atropine and generally are not as effective. Anticholinergic agents can produce side effects, including mydriasis and constipation.

Alternatively, a sympathomimetic agent can be administered. Terbutaline and albuterol syrup are the two choices. Sympathomimetic drugs act indirectly by counteracting the effects of increased vagal tone. They can produce side effects, including hyperactivity and tachycardia. Dosage adjustment may reduce the side effects while maintaining efficacy. Dogs that have intolerable side effects or that are unresponsive to medical therapy should have a pacemaker implanted. The pacemaker will prevent clinical signs that occur secondary to sinus arrest.[1]

45.8 ATRIAL STANDSTILL

45.8.1 Definition, Causes, and Electrocardiographic Findings

Atrial standstill is the rhythm diagnosis when no P waves are visible on the ECG and atrial fibrillation is not evident (Figure 45-1). Atrial standstill occurs when the atrial myocardium is unable to depolarize. This occurs for two broad general reasons: (1) either the atrial muscle is destroyed by disease or (2) the serum potassium concentration is increased to a level at which the resting membrane potential of atrial cells is so low (i.e., closer to zero) that they no longer depolarize.

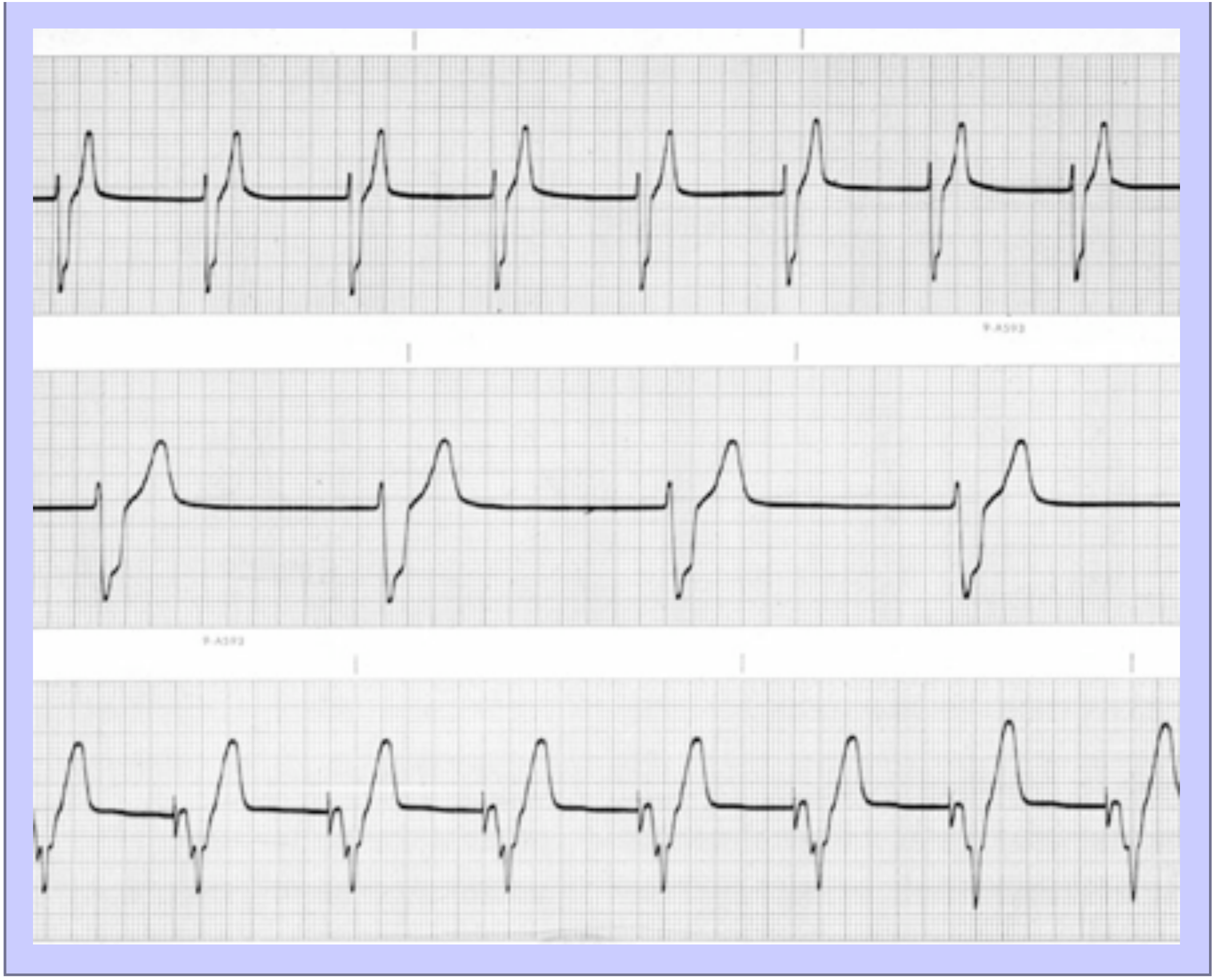
In the former, a particular type of cardiomyopathy or myocarditis destroys atrial myocardium and replaces it with fibrous tissue. In this disease, the internodal tracts and the sinus node apparently are also destroyed. Consequently, the AV junctional tissue takes over the pacing function of the heart. These dogs present with heart rates usually in the 40- to 60-beats/min range. A pacemaker can be implanted to control signs of episodic weakness or syncope. Pacemaker implantation may also improve signs of heart failure by increasing cardiac output through the increase in heart rate (see Figure 45-1). Long-term prognosis for these dogs is usually poor because of progressive AV valve regurgitation and ventricular myocardial dysfunction.[1]

In dogs or cats with moderate to severe hyperkalemia, the atrial myocardium loses its ability to depolarize (Figure 45-2). The sinus node and ventricular myocardium retain the ability to depolarize until even higher potassium concentrations are achieved. Moderate to severe hyperkalemia results in a sinoventricular rhythm in which the sinus node controls the electrical activity of the heart. Sinus node depolarization is carried through the internodal tracts to the AV node and the ventricles, and because the atrial myocardium does not depolarize, no P waves are generated on the ECG. Hyperkalemia also causes slowed depolarization of the sinus node and ventricular myocardium, resulting in a sinus bradycardia and prolonged QRS complexes.[1]

45.9 ATRIOVENTRICULAR BLOCKS

AV block refers to conduction disturbances that alter conduction of the cardiac electrical impulse from the sinus node to the ventricles. Altered intraatrial conduction, altered AV junctional conduction, altered bundle of His conduction, and altered conduction in both bundle branches simultaneously can alter AV conduction. AV blocks are classified as first-degree, second-degree, and third-degree AV blocks.[1]

Figure 45-1 Lead II electrocardiogram tracings from a dog that was presented for being lethargic for 1 month and that had had ascites for the previous 2 weeks. The heart rate was 50 to 60 beats/min on auscultation. There are no P waves visible in the top and middle tracings. The top tracing is recorded at 25 mm/sec, and the middle trace is recorded at 50 mm/sec paper speed. The ventricular rate is 55 beats/min and regular. These features are characteristic of atrial standstill. The QRS complexes are wide and bizarre in appearance. The configuration of the QRS complexes indicates that the escape focus in this dog is either in Purkinje fibers (ventricular escape beats) or in the atrioventricular junctional tissue and not conducted in the right bundle branch (nodal escape rhythm with a right bundle branch block). Because the rate is consistent with a nodal escape rhythm, the escape focus is most likely in the atrioventricular junctional tissue. The bottom tracing was recorded at 50 mm/sec after pacemaker implantation. The generator was set at a rate of 100 beats/min. A sharp deflection precedes each QRS complex. This is a so-called *pacemaker spike* that occurs when the generator produces its electrical signal. The pacemaker spikes are exactly 0.6 second apart, indicating that the set rate (100 beats/min) is being produced. The QRS complexes are wide and bizarre in appearance, because the wave of depolarization originates within myocardium and must conduct from muscle cell to muscle cell. (1 cm = 1 mV.) (From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.) From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.



45.9.1 First-Degree Atrioventricular Block

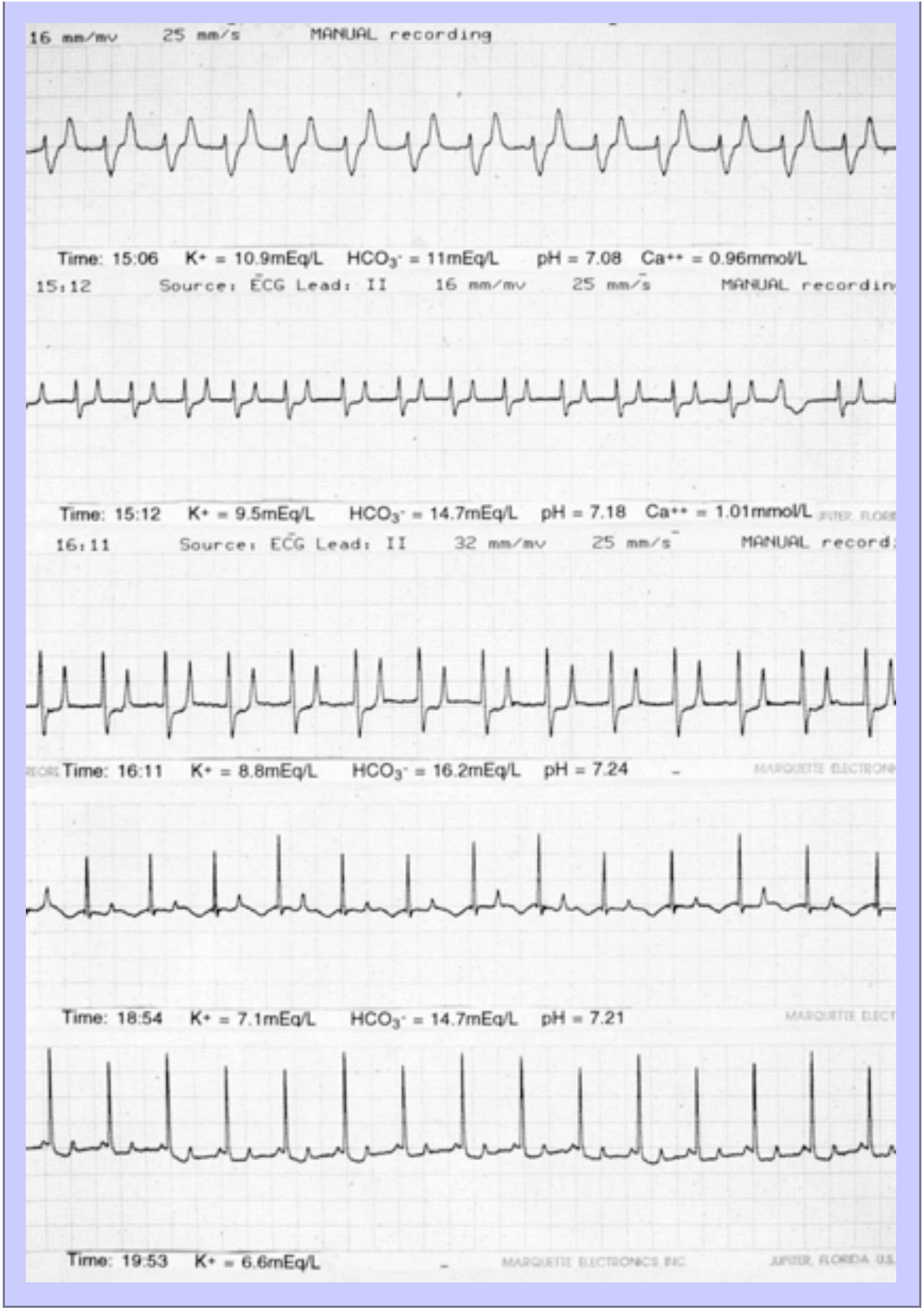
45.9.1.1 Definition and Electrocardiographic Diagnosis

First-degree AV block occurs when the conduction time from the sinus node to the ventricles is prolonged beyond normal, causing a prolongation in the PR interval. It does not result in an arrhythmia. First-degree AV block is diagnosed when the PR interval is longer than 0.13 second in a dog and longer than 0.09 second in a cat. It can occur as an isolated abnormality or may be present in conjunction with second-degree AV block (Figure 45-3).

45.9.1.2 Causes

First-degree AV block can occur because of degenerative or inflammatory disease of the conduction system. It can also occur secondary to drug administration (e.g., digitalis glycosides, β-blockers, calcium channel blockers), hyperkalemia, and increased vagal tone.[1]

Figure 45-2 Sequential electrocardiogram tracings from a cat with anuric renal failure, severe hyperkalemia, and metabolic acidosis before *(top tracing)*, during (middle three tracings), and after *(bottom tracing)* hemodialysis. The top tracing (serum potassium concentration = 10.9 mEq/L) shows a slow heart rate or approximately 100 beats/min, a wide QRS complex, and no P waves. As the potassium concentration decreases, the QRS complex duration decreases, the heart rate increases, and the T waves become large and "tented." The QRS complexes and T waves normalize at a potassium concentration of 7.1 mEq/L, and P waves reappear when the potassium concentration reaches 6.6 mEq/L. (From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.) From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.


16 mm/mv 25 mm/s MANUAL recording
Time: 15:06 K+ = 10.9mEq/L HCO3- = 11mEq/L pH = 7.08 Ca++ = 0.96mmol/L
15:12 Source: ECG Lead: II 16 mm/mv 25 mm/s MANUAL recordin
Time: 15:12 K+ = 9.5mEq/L HCO3- = 14.7mEq/L pH = 7.18 Ca++ = 1.01mmol/L
16:11 Source: ECG Lead: II 32 mm/mv 25 mm/s MANUAL record
Time: 16:11 K+ = 8.8mEq/L HCO3- = 16.2mEq/L pH = 7.24
MARQUETTE ELECTRON
Time: 18:54 K+ = 7.1mEq/L HCO3- = 14.7mEq/L pH = 7.21
MARQUETTE ELECT
Time: 19:53 K+ = 6.6mEq/L
MARQUETTE ELECTRONICS INC
JUPITER, FLORIDA U.S.

45.9.1.3 Prognosis

The prognosis for first-degree AV block is good to guarded. First-degree AV blocks that occur secondary to drug administration and electrolyte abnormalities disappear when these abnormalities are corrected. First-degree AV blocks secondary to increased vagal tone result in no clinical sequelae. Degenerative disease of the conduction system mild enough to produce only first-degree AV block often does not progress; however, it may, on occasion, progress to higher degrees of AV block. No treatment is necessary for first-degree AV block.[1]

45.9.2 Second-Degree Atrioventricular Block

45.9.2.1 Definition and Electrocardiographic Diagnosis

Second-degree AV block occurs when some sinus depolarizations conduct through the AV junction to reach the ventricles and others do not. On auscultation it is heard as “dropped beats.” Second-degree AV block produces an abnormal heart rhythm. It can range in severity from only an occasional P wave not followed by a QRS complex on the ECG to most P waves being blocked.

Figure 45-3 Lead II electrocardiogram tracing recorded from a dog that presented because of repeated episodes of syncope. The PR interval is markedly prolonged to 0.36 second (first-degree atrioventricular [AV] block). The rhythm is a second-degree AV block that varies between 3:1 and 2:1 AV block. The atrial rate is reasonably constant at approximately 80 beats/min. When there is a 2:1 block, the ventricular rate is approximately 40 beats/min. When the block is 3:1 it is approximately 27 beats/min. This is an example of first-degree AV block and high-grade second-degree AV block. Atropine administration increased the atrial rate but did not change the ventricular rate. A pacemaker was implanted. (Paper speed = 25 mm/sec; 1 cm = 1 mV.) (From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.) From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.

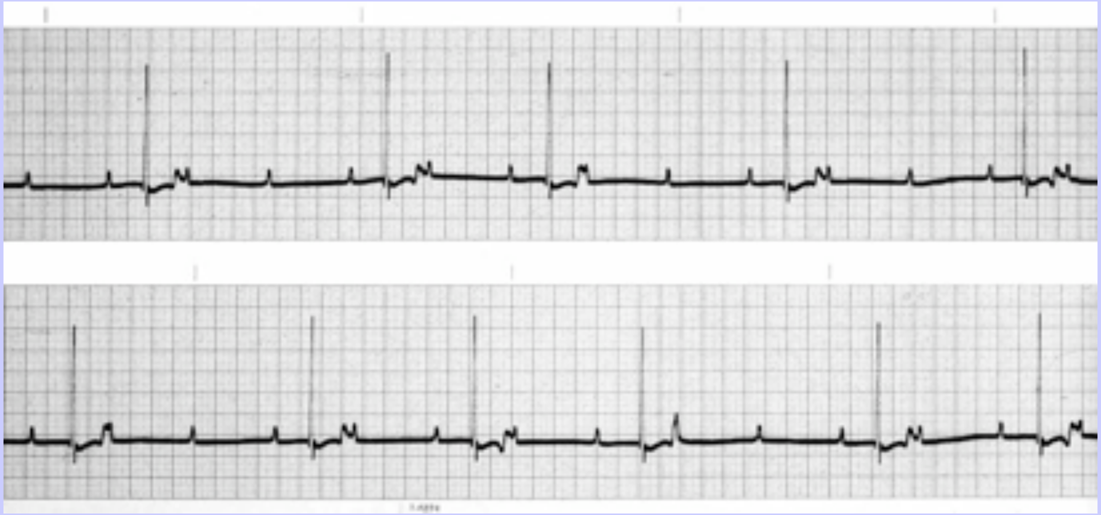
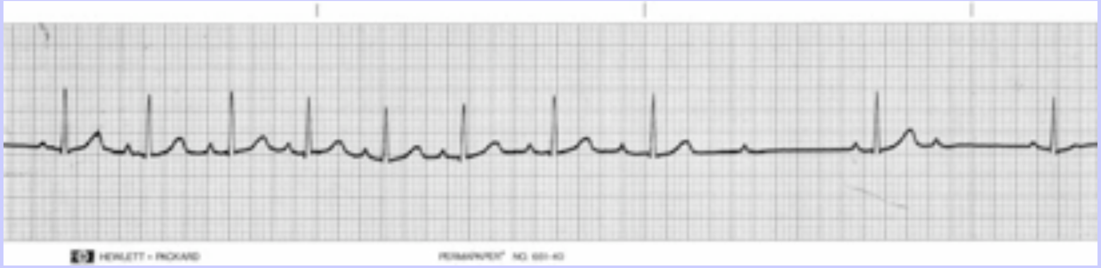


Figure 45-4 Lead II electrocardiogram tracing recorded from a dog with chronic respiratory disease and an arrhythmia. The ninth P wave is not followed by a QRS complex. Before this so-called *dropped beat,* the PR interval prolongs and then shortens immediately after the block. This is an example of a Mobitz type I (type I or Wenckebach) second-degree atrioventricular block. This type of atrioventricular block is usually vagally induced and can be abolished with atropine administration. (Paper speed = 50 mm/sec; 1 cm = 1 mV.) (From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.) From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.



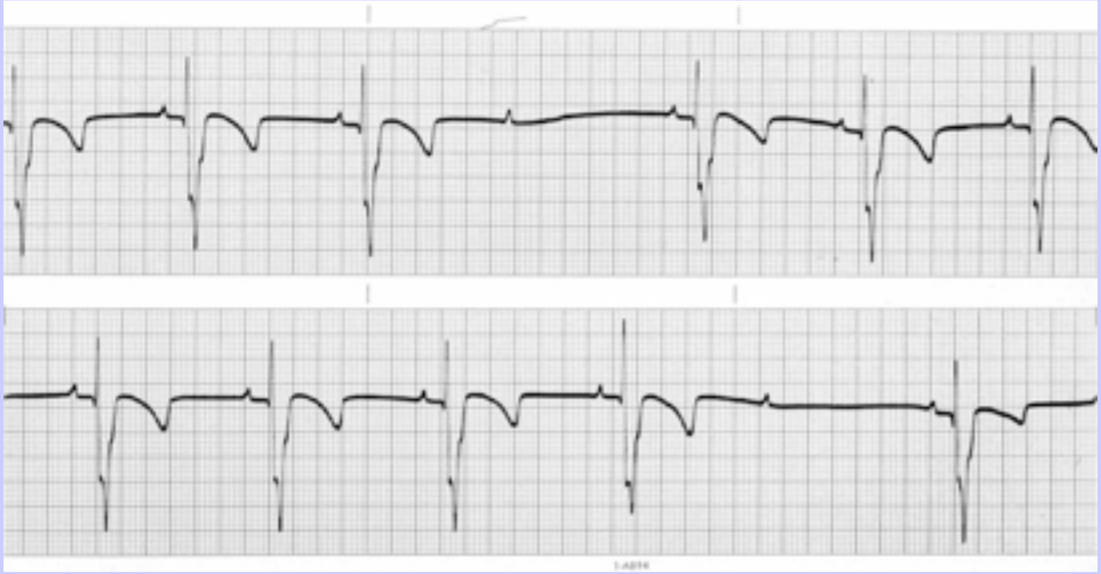
Second-degree AV block is divided into type I, type II, and high-grade blocks. In a type I (Mobitz type I), or Wenckebach, second-degree AV block, the PR interval progressively prolongs before the blocked beat (Figure 45-4). The PR interval before the block may be normal or too long (first-degree AV block). Type II (Mobitz type II) second-degree AV block is characterized by sudden failure of conduction without alteration in the PR interval (Figure 45-5). The PR interval may be normal or prolonged. Second-degree AV blocks commonly are labeled with the number of P waves followed by the number of QRS complexes generated. For example, if every other sinus depolarization is blocked from reaching the ventricles, this is called a 2:1 second-degree AV block. Similarly, if every fourth P wave is not followed by a QRS complex, it is called a 4:3 AV block (four P waves and three QRS complexes). Any block that is 2:1 or greater cannot be classified as type I or type II because there is no chance to determine whether progressive prolongation is occurring or not. Consequently, it is called a *high-grade block* (see Figure 45-3).[1]

45.9.2.2 Mechanisms

Second-degree AV block can be a normal finding (functional second-degree AV block). The normal AV node 192
prevents rapid impulses from being transmitted to the ventricles. This type of functional block is extremely 193
important in patients with atrial fibrillation or atrial flutter. If the AV junction were not present, atrial

fibrillation and flutter would conduct 1:1 to the ventricles, resulting in ventricular fibrillation and immediate death.

Figure 45-5 Lead II electrocardiogram tracing recorded from a dog that presented with an arrhythmia. This is a sinus rhythm with intermittent periods of second-degree atrioventricular (AV) block. The PR interval does not change before or after the block, so this is a Mobitz type II (type II) second-degree AV block. The QRS complex configuration is abnormal (deep and wide S waves), and the complexes are too wide. The mean electrical axis and the terminal axis were shifted to the right. Consequently, the diagnosis was a type II second-degree AV block with a right bundle branch block. This dog progressed to a third-degree AV block, developed syncope, and an artificial pacemaker was implanted. (Paper speed = 50 mm/sec; 1 cm = 1 mV.) (From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.) From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.



As with first-degree AV block, conduction abnormalities in any region of the conduction system can create second-degree AV block. Few studies have been performed to delineate the exact sites of block in dogs or cats with second-degree AV block. Most type I second-degree AV blocks are caused by drug toxicity, physiologic changes, or disease within the AV node itself. One study in dogs, however, has documented type I second-degree AV block in dogs with His bundle pathology created by ischemia.[5]

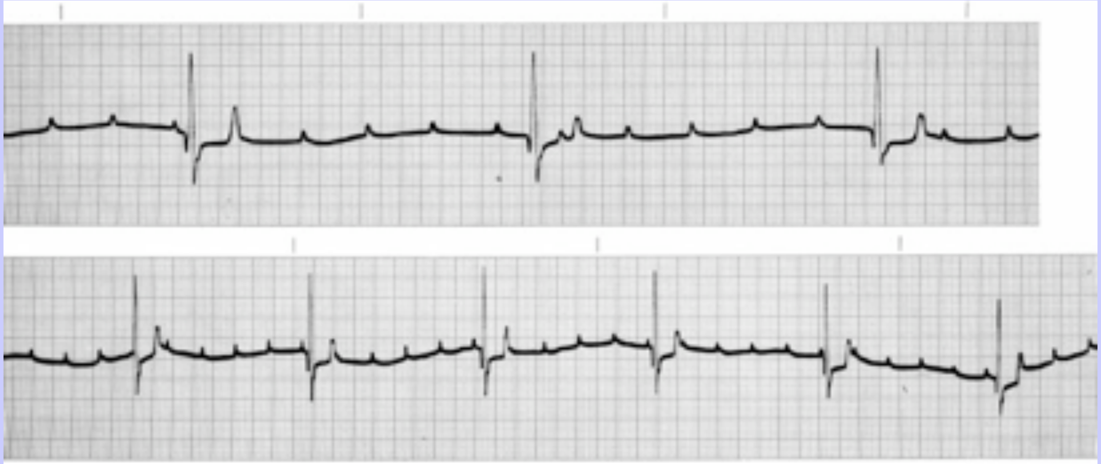
45.9.2.3 Causes

Second-degree AV block can be observed in normal dogs, especially in puppies 8 to 11 weeks of age.[6] This normal finding occurs only at rest and is a Mobitz type I block. The presence of second-degree AV block in a dog in an examination room is almost always abnormal. It can occur secondary to increased vagal tone. The AV node is richly innervated with vagal fibers. Consequently, increased vagal tone usually produces a type I rather than a type II second-degree AV block. Chronic respiratory disease is a common cause of second-degree AV block secondary to increased vagal tone in dogs. Digitalis is an example of a drug that can produce second-degree AV block, primarily through its ability to increase vagal tone. Other drugs that can cause second-degree AV block via vagal stimulation include xylazine and intravenous atropine. The increase in vagal tone with intravenous atropine occurs before the decrease in vagal tone and is transient. Second-degree AV block can also be due to conduction system disease.

45.9.2.4 Treatment

Patients with type I or type II second-degree AV blocks generally do not exhibit any clinical signs. Consequently, usually no treatment is necessary for these patients except to remove an inciting cause if one exists. Dogs with high-grade second-degree AV block may not exhibit any clinical signs or may have signs identical to dogs with third-degree AV block (primarily syncope and weakness). Treatment for these patients is described in the next section[1] (see Figure 45-3).

Figure 45-6 Lead II electrocardiogram tracings recorded from a dog that was presented with syncope. The P waves and the QRS complexes are dissociated (atrioventricular dissociation), as evidenced by the varying PR intervals. The sinus rate (approximately 180 beats/min) is faster than the ventricular rate (35 beats/min). These characteristics are diagnostic of third-degree atrioventricular block. The ventricular rate suggests that the escape rhythm originates in the Purkinje fibers. The QRS duration, however, is normal, which means that the escape focus must be in the atrioventricular junction. (*Top,* Paper speed = 50 mm/sec; 1 cm = 1 mV. *Bottom,* Paper speed = 25 mm/sec; 1 cm = 1 mV.) (From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.) From Kittleson MD: Diagnosis and treatment of arrhythmias [dysrhythmias]. In Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine,* St Louis, 1998, Mosby.



45.9.3 Third-Degree Atrioventricular Block

45.9.3.1 Definition and Electrocardiographic Diagnosis

Third-degree AV block (complete heart block) occurs when there is no conduction between the sinus node and the ventricles (Figure 45-6). In third-degree AV block, the sinus node depolarizes at its own inherent rate, depolarizing the atria and producing P waves, whereas the ventricles are depolarized by a subsidiary pacemaker (either the AV node or Purkinje fibers) that depolarizes at a slower rate, depolarizing the ventricles and producing QRS complexes. On the ECG, there is no relationship between the P waves and QRS complexes (AV dissociation), resulting in varying PR intervals from beat to beat (see Figure 45-6). The atrial rate and the ventricular rate are often constant such that the P-P intervals and the R-R intervals are constant.[1]

45.9.3.2 Causes

The cause of third-degree AV block in almost all cases is unknown. Most affected canine and feline patients are middle-age to geriatric patients. This may suggest a degenerative disease of the conduction system. Rarely, a dog younger than 1 year of age will have third-degree AV block that may be congenital. Third-degree AV block has been reported in one dog with myocarditis that was seropositive for Lyme disease.[7]

AV block also has been described in humans with Lyme carditis. The AV block in this disease is usually transient. Occasionally, third-degree AV block in dogs will resolve spontaneously or will resolve after glucocorticoid administration, suggesting an inflammatory lesion in the conduction system.[1] It is interesting to speculate that this situation could be secondary to Lyme carditis, but there is no evidence to support this.

AV nodal disease has been described in dogs that have died suddenly. Lesions described include mineralization of the crest of the interventricular septum, with degeneration and fibrosis of the AV conduction fibers and cartilage and bone formation in the central fibrous body.[8] Doberman Pinschers appear to be overrepresented in the group of dogs described with these findings.[9]

45.9.3.3 Clinical Signs

Dogs with third-degree AV block generally either have no clinical signs or are presented because they are having episodes of syncope. Most cats have no clinical signs of their disorder. In general, clinical presentation depends on the underlying heart rate. Dogs generally fall into two categories: those with a ventricular rate between 40 and 60 beats/min and those with a heart rate between 20 and 40 beats/min. His bundle escape rhythms typically have a rate of 35 to 65 beats/min, so the AV node is likely the site of the block in dogs with this heart rate (see Figure 45-6).

Apparently, the subsidiary pacemakers in cats depolarize at a rate faster than those of dogs and humans. Cats with third-degree AV block generally have a ventricular rate of 80 to 130 beats/min. Because cats' ventricular rates are generally quite fast and because cats are usually sedentary, those with third-degree AV block usually do not exhibit any clinical signs.[1]

45.9.3.4 Clinical Findings

On physical examination, most dogs with third-degree AV block appear normal between syncopal events. However, in some dogs the heart rate is slow enough to produce signs of weakness. In dogs that appear weak, measuring whole blood lactate concentration may be helpful. In many of these dogs it is increased, signifying inadequate oxygen delivery to systemic tissues because of a low cardiac output.

On auscultation, the heart rate is slow and the first heart sound may be loud. By listening carefully in a quiet room, one can often identify soft fourth heart sounds in the background. These sounds are generated each time the atria contract. Cannon *a* waves may be generated in the jugular veins when atrial contraction occurs when the mitral valve is closed.[1]

45.9.3.5 Treatment

Treatment of third-degree AV block is implantation of an external pacing generator and lead (artificial pacemaker). Some dogs with very slow heart rates (usually less than 30 beats/min) are very weak, and some are unable to stand at presentation. In these dogs, measuring blood lactate concentration is recommended. If it is increased, place a temporary pacemaker, implant a permanent pacemaker on an emergency basis, or administer isoproterenol as a constant rate intravenous infusion to increase the heart rate until a permanent pacemaker can be implanted. Isoproterenol infusion is generally safe, but tachyarrhythmias and hypotension secondary to systemic arteriolar dilation can be produced.[1]

45.10 BUNDLE BRANCH BLOCKS

The left and right bundle branches originate in the bundle of His. Their function is to spread the cardiac electrical impulse rapidly to the Purkinje fibers in both ventricles and to coordinate the depolarization of the ventricles. The bundle branches, like the rest of the conduction system, cannot be seen on gross examination.[1]

Ventricular depolarization is abnormal in bundle branch blocks. Normally the cardiac electrical impulse proceeds from the AV node through the bundle of His, and then rapidly down both left and right bundle branches to the Purkinje fibers. The bundle branches spread the cardiac electrical impulse to both ventricles rapidly. If a bundle branch cannot conduct to a particular ventricle, conduction to that ventricle still occurs. However, the impulse must travel from muscle cell to muscle cell. This is a much slower process. Consequently, if a bundle branch is unable to conduct the cardiac electrical impulse, conduction to the unaffected ventricle is normal and conduction to the ventricle served by the abnormal bundle branch is delayed. Complete block of both the right and left bundle branches produces complete (third-degree) AV block.

Bundle branch blocks are usually persistent. However, they can also be intermittent (i.e., the QRS morphology is normal at times and abnormal at other times).[10] Intermittent bundle branch blocks are most commonly rate related; they occur at certain heart rates but not at others. Bundle branch blocks can occur when the heart rate increases or decreases to a certain level, but most commonly they emerge at faster heart rates. In this situation, at least some cells in a bundle branch must have a prolonged refractory period.[11]

45.10.1 Right Bundle Branch Block

Right bundle branch block (RBBB) can be complete or incomplete; it occurs because of conduction system disease or secondary to right ventricular enlargement. Rarely, a dog can have a congenital RBBB. The cause of most conduction system disease in dogs and cats is unknown. At the time of diagnosis, all that can be seen histologically are degenerative changes. Because conduction time is so prolonged, the QRS complex is wider than normal (longer than 0.06 second in the dog and longer than 0.04 second in the cat). RBBB causes decreased R wave amplitude and large, wide S waves in leads I, II, III, and aVF.

RBBB by itself does not cause clinical sequelae. Dogs can have a congenital RBBB, be normal clinically, and live a normal life span.[10] The only hemodynamic abnormality produced by a RBBB is delayed activation of the right ventricle and a prolonged right ventricular ejection time (the time it takes to eject blood in systole). This results in delayed closure of the tricuspid and pulmonic valves and can result in split heart sounds, most commonly a split second heart sound.[10]

45.10.2 Left Bundle Branch Block

The left bundle branch is a fan-shaped network of interwoven fibers. Complete disruption of the left bundle branch results in delayed depolarization of the left ventricle. Because the left ventricle can no longer be depolarized from the left bundle branch, depolarization must proceed down the right bundle branch and across the interventricular septum to the left ventricle. In this situation the initial depolarization of the ventricles is relatively normal and may produce a small Q wave. After this, the left ventricular depolarization wave predominates like it normally does. Consequently, the orientations of the QRS complexes on the ECG are normal (there is no change in the mean electrical axis).

Because of the delayed left ventricular activation, one major change noted in the QRS complex is an increase in its duration (it is wider than normal). The other major change that commonly occurs is an increase in the R wave height in the lead most parallel with the left ventricular depolarization wave (usually lead II). Besides abnormal ventricular depolarization, ventricular repolarization is also abnormal in left bundle branch block (LBBB). The T wave in LBBB is always large and opposite in polarity to the QRS complex.[1]

LBBB occurs secondary to degenerative conduction system disease, left ventricular myocardial disease, or diseases that produce severe left ventricular hypertrophy. Because the left bundle branches early and widely throughout the left ventricle, LBBB usually indicates widespread disease. LBBB almost never occurs by itself as a benign abnormality.[1]

45.11 SUGGESTED FURTHER READING[*]

GR Bolton, SJ Ettinger: Right bundle branch block in the dog. *J Am Vet Med Assoc*. **160**, 1972, 1104, *An excellent veterinary paper that describes the variations in morphology that one can see with RBBB in the dog (e.g., QRS morphology that can be normal at times and abnormal at other times)*.

CE Branch, BT Robertson, JC Williams: Frequency of second-degree atrioventricular heart blocks in dogs. *Am J Vet Res*. **36**, 1975, 925, *An excellent veterinary paper that describes the frequency and breed associations of second-degree AV blocks in dogs*.

MD Kittleson: Electrocardiography, diagnosis and treatment of arrhythmias. In MD Kittleson, RD Kienle (Eds.): *Small animal cardiovascular medicine*. 1998, Mosby, St Louis, *Classic textbook of clinical cardiology. Excellent chapter that provides in-depth information for understanding the basic pathophysiologic mechanisms of bradyarrhythmias in the context of an excellent reference textbook on cardiovascular medicine*.

D Sisson, M Oyama: In *Cardiovascular medicine of companion animals. Course outline for cardiovascular medicine*. 2003, University of Illinois School of Veterinary Medicine, Champagne Urbana, IL, *Excellent overview of cardiovascular physiology and medicine; personal communication with authors. Not available in print*.

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[*] See the CD-ROM for a complete list of references

46 Chapter 46 Supraventricular Tachyarrhythmias

Kathy Wright, DVM, DACVIM (Cardiology and Small Animal Internal Medicine)

46.1 KEY POINTS

- Supraventricular tachyarrhythmias (SVTs) are rapid rhythms originating from or dependent on tissues above the ventricles.
- Once thought relatively benign, SVTs are an important cause of morbidity, and even mortality, in small animals.
- Recognition of underlying structural heart disease and the contribution of SVTs to myocardial dysfunction are critical for accurate patient treatment.
- Acute termination of SVTs should be accomplished by medical means, based on the likely mechanism of the tachyarrhythmia. Drugs that slow atrioventricular (AV) nodal conduction often are combined with those that suppress an abnormal atrial or nodal focus or interrupt a reentrant circuit within an accessory pathway or the atria.
- Long-term management can include antiarrhythmic therapy or procedures to eliminate an abnormal electrical circuit (such as an accessory pathway). Individual responses to antiarrhythmic drugs, both therapeutic and adverse effects, must be monitored carefully, with individual adjustments made accordingly.

46.2 INTRODUCTION

SVTs are defined as rapid cardiac rhythms that (1) originate in the atria or AV junction (above the bundle of His) or (2) involve the atria or AV junction as a critical component of a tachyarrhythmia circuit.[1] The most clinically useful classification system broadly groups SVTs into atrial tachyarrhythmias or AV nodal–dependent tachyarrhythmias.[2] Such classification helps us to guide therapy of these abnormal heart rhythms and is discussed in detail later in this chapter.

The importance of managing SVTs has become clearer in recent years. Not only can these abnormal rhythms result from structural heart disease, but they can be the cause of structural heart disease, as well. Pacing studies and clinical cases have demonstrated that sustained or frequently occurring SVTs can result in a poorly functioning, dilated heart.[3–6] This is known as *tachycardiomyopathy* or *tachycardia-induced cardiomyopathy* and cannot be distinguished initially from idiopathic dilated cardiomyopathy. Tachycardiomyopathy, however, can be partially or completely reversible with adequate rhythm control. It is the most frequently unrecognized curable cause of heart failure in human (and likely veterinary) patients.[4] SVTs can also result in sudden death, although less frequently than does sustained ventricular tachycardia. Sudden death has occurred in a number of dogs with sustained tachyarrhythmias secondary to accessory pathways. The presumed mechanism is myocardial ischemia that gives rise to ventricular tachycardia and fibrillation, although the sudden onset of electromechanical dissociation has been seen in two dogs.

46.3 HISTORICAL DATA

Careful questioning of owners should be pursued to try to determine clinical signs that may be related to an SVT or structural heart disease. Those commonly reported include decreased exercise tolerance, weakness, collapse, gastrointestinal (GI) signs (particularly vomiting and inappetence), noticeably rapid heart rate (most evident when the animal is in lateral recumbency), and pulsing of the ears or bobbing of the head with each heart beat. Several animals were diagnosed initially as having primary GI disease, only to find later that their GI signs were related to an SVT. Signs reported by owners whose animals have developed congestive heart failure include dyspnea, tachypnea, and abdominal distention. Some owners believe that their dogs are asymptomatic, only to realize how affected they have been once the tachyarrhythmias is controlled.

46.4 PHYSICAL EXAMINATION FINDINGS

It is important to remember that at the time an animal with SVT is presented to the veterinarian, the physical examination findings may be normal if the SVT was paroxysmal. On the other hand, a tachyarrhythmia may be detected at the time of arrival or while the animal is hospitalized. Decreased systemic arterial pulse quality, mucous membrane pallor, a peritoneal fluid wave, tachypnea or dyspnea with auscultable pulmonary abnormalities, murmurs of mitral or tricuspid regurgitation secondary to tachycardiomyopathy, and murmurs associated with a primary underlying heart disease are all potential physical examination findings.

46.5 EXAMINING THE ELECTROCARDIOGRAM

46.5.1 Distinguishing Supraventricular from Ventricular Tachyarrhythmias

It is most important to distinguish ventricular tachyarrhythmias from SVTs because the treatment and differential diagnoses for each will differ. A narrow QRS complex tachyarrhythmia will almost always be an SVT. The vast majority of wide complex tachyarrhythmias are ventricular tachyarrhythmias. Up to 80% of wide complex tachyarrhythmias in human case series are ventricular in origin.[7] If the patient has prior ECGs when in sinus rhythm or exhibits conversion, even briefly, to sinus rhythm during the tachyarrhythmia, the QRS complexes can be compared with those during tachyarrhythmia. Preexisting bundle branch block can thus be identified. Distinguishing ventricular arrhythmias from SVTs with bundle branch aberration that develops during SVT or antegrade conduction of a tachycardia over an accessory pathway (very rare in companion animals) is the most difficult task for the clinician. No criteria are absolute; however, the following rules are helpful[7,8]:

1. Identification of P′ waves (representing atrial depolarization that originates outside the sinoatrial node) with a consistent relationship to the QRS is indicative of an SVT with aberration. In dogs undergoing electrophysiologic studies, retrograde AV nodal conduction is rare and has a long effective refractory period when it does occur. As many leads as possible should be run to identify P′ waves. Lewis leads, using the right and left arm electrodes of the standard ECG placed on various positions over the precordium while monitoring the lead I channel, are very helpful in identifying P′ waves.

2. QRS fusion complexes are a hallmark of ventricular tachyarrhythmia.

3. If the tachycardia terminates in response to a vagal maneuver, this indicates that the tachycardia is supraventricular in origin. If the tachycardia does not terminate with a vagal maneuver, it may be of either supraventricular or ventricular origin.

4 If the tachycardia terminates with the administration of intravenous lidocaine, this diagnostic and therapeutic procedure indicates that the wide complex tachyarrhythmia is much more likely ventricular in origin.

46.5.2 Diagnosing Atrial Versus Atrioventricular Node–Dependent Tachyarrhythmias

Once an SVT has been identified, it is helpful to determine if it is atrial or AV node dependent. If the SVT is irregularly irregular and no organized atrial activity is identifiable, then atrial fibrillation is the diagnosis. Differentiation of regular SVTs involves several steps. Initiation and termination of the SVT are important diagnostic features. If an SVT continues despite AV block, it is atrial in origin. If a premature ventricular contraction terminates the SVT, it is far more likely that it is an AV node–dependent tachyarrhythmia. If a vagal maneuver terminates the SVT, it is also far more likely an AV node–dependent tachyarrhythmia.

Identification of P′ waves is an important diagnostic step, but it can be difficult in a rapid SVT. Precordial and Lewis leads help with their identification. The relationship of the P′ wave to the preceding QRS complex relative to the total R-R interval identifies an SVT as either a short RP′ (RP′ interval ≤50% of the RR interval) or a long RP′ (RP′ interval >50% of the RR interval) SVT.[1] Important identifying characteristics and mechanisms of the more common SVTs are reviewed in Table 46-1 and Figure 46-1. The most commonly occurring SVTs in small animals appear to be atrial fibrillation, intraatrial reentrant tachycardia, orthodromic AV reciprocating tachycardia (a macroreentrant circuit in which an impulse is carried from the atria to the AV node–His-Purkinje system to the ventricles to a retrograde-conducting accessory pathway to the atria), and automatic atrial tachycardia. Because the retrograde conduction properties of the canine AV node are poor, AV nodal reentrant tachycardia has not been identified in dogs undergoing electrophysiologic study for clinical tachyarrhythmias.

46.6 TREATMENT OF SUPRAVENTRICULAR TACHYARRHYTHMIAS

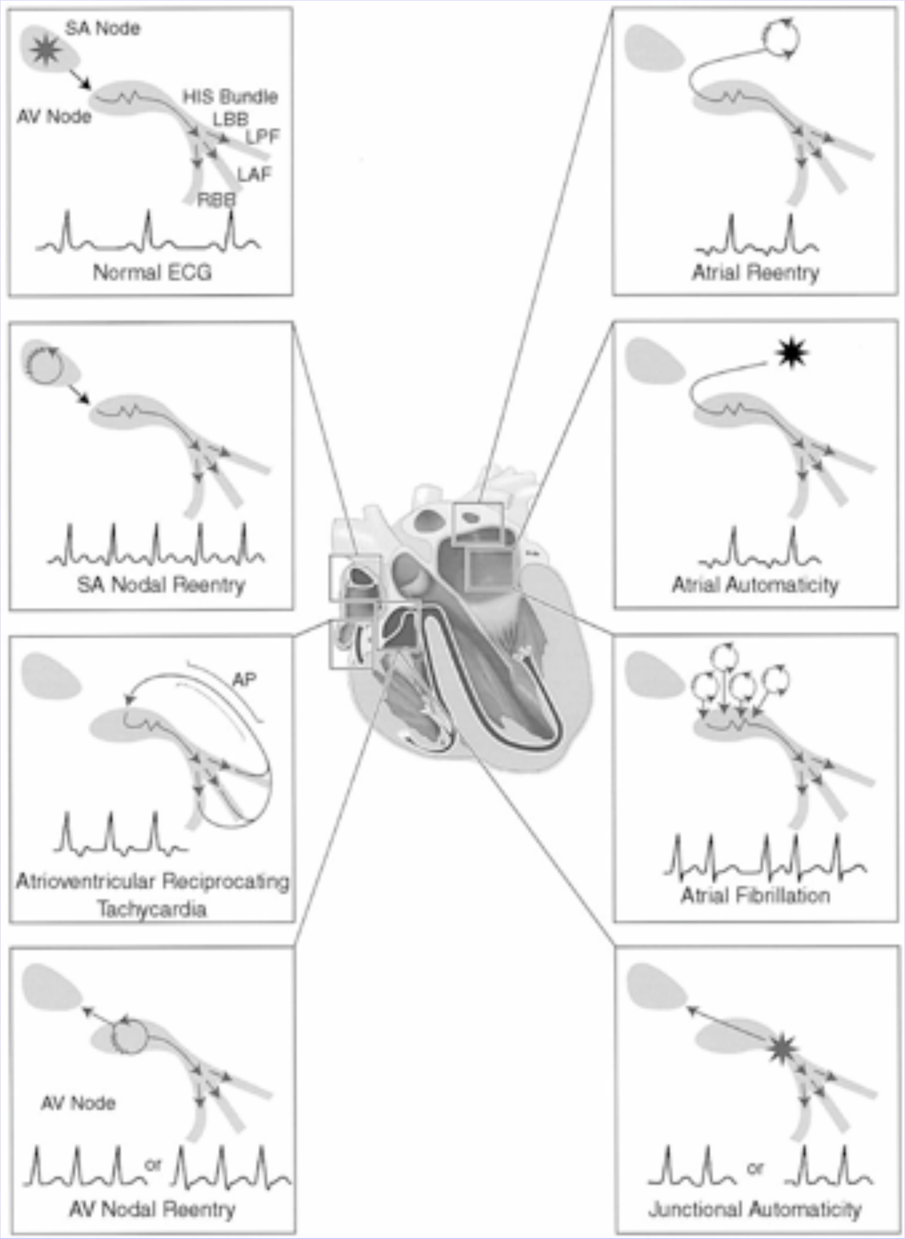
It is essential to identify predisposing factors that are contributing to the initiation or perpetuation of SVT in a given patient. Acid-base abnormalities, electrolyte disturbances, significant anemia, and hypoxemia should be corrected. AV node–dependent tachyarrhythmias are treatment in some cases by single-agent therapy aimed at interrupting conduction through the AV node. Other AV node–dependent SVTs require that an additional drug be added to suppress another site in the circuit. Atrial tachyarrhythmias are best addressed by dual therapy: one drug to slow AV nodal conduction and a second drug to inhibit the atrial automatic focus or interrupt conduction in an atrial reentrant circuit. Sites of antiarrhythmic drug action in SVT are shown in Figure 46-2.

Table 46-1 Characteristics of Common Supraventricular Tachyarrhythmias

SVT Mechanism	P′ Waves Visible?	P′ Wave Morphology	RP′ vs. RR Interval	Initiation and Termination	Response to AV Block
ATRIAL					
Automatic atrial	Yes	Variable, differs from sinus P	Varies with SVT rate, often long	Gradual rate acceleration and deceleration	SVT continues
Intraatrial reentry	Yes	Variable, differs from sinus P	Varies with SVT rate, often long	Abrupt onset and offset at SVT rate	SVT continues
Atrial flutter	*f* Waves	Identical saw-toothed F waves	Not applicable	Abrupt onset and offset at SVT rate	SVT continues
Atrial fibrillation	No, *f* waves may be seen	No visible P waves; *f* waves may be seen	Not applicable	Abrupt onset and offset at SVT rate, often incessant	SVT continues
AV NODE–DEPENDENT					
OAVRT	Often visible within ST-T segment	Retrograde: (–) in II, III, avF	Typically short	Abrupt onset and offset	SVT terminates
Automatic junctional	Generally yes; AV dissociation common	Variable	Variable	Gradual rate acceleration and deceleration	SVT continues with AV dissociation
AV nodal reentry	Generally no	Retrograde: (–) in II, III, avF	Short	Abrupt onset and offset	SVT terminates

AV, Atrioventricular; *OAVRT,* orthodromic atrioventricular reciprocated tachycardia; *SVT,* supraventricular tachycardia.

Figure 46-1 Representation of the mechanisms and electrocardiographic characteristics of the more common supraventricular tachyarrhythmias. *AP,* Accessory pathway; *AV,* atrioventricular; *ECG,* electrocardiogram; *LAF,* left anterior fascicle; *LBB,* left bundle branch; *LPF,* left posterior fascicle; *RBB,* right bundle branch; *SA,* sinoatrial. From Bonagura JD: *Kirk's current veterinary therapy XIII,* ed 13, Philadelphia, 2000, Saunders.



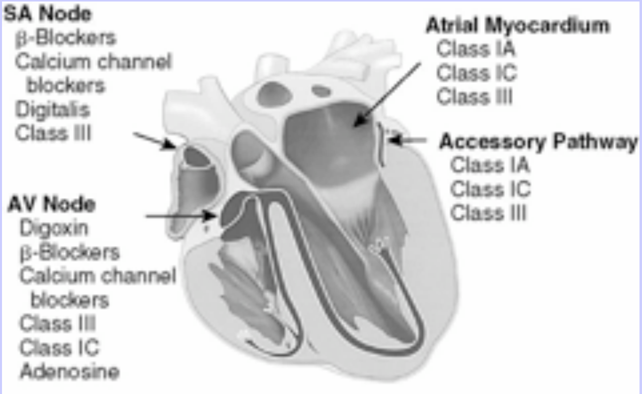
46.6.1 Emergent Therapy

Animals in incessant, rapid SVT require interruption of the tachyarrhythmia. Vagal maneuvers may be tried first and may terminate the SVT if it is AV node dependent. Subjectively, the most effective vagal maneuver in small animals is carotid sinus massage. Sustained, gentle compression is applied for 5 to 10 seconds over the carotid sinus, which is located immediately caudal to the dorsal aspect of the larynx. The ECG needs to be monitored continuously throughout the procedure. More often, however, the SVT does not terminate with such maneuvers and drug therapy must be initiated.

Parenteral negative dromotropic agents can be used to interrupt a tachyarrhythmic circuit that uses the AV node and is causing hemodynamic compromise. In atrial tachyarrhythmias, such agents will not terminate the arrhythmia but will slow conduction to the ventricles. Intravenous calcium channel blockers, β-blockers, or adenosine have been used for this purpose. Blood pressure and ECG should be monitored before and throughout the procedure.

A comparison of the electrophysiologic and hemodynamic responses of intravenous diltiazem, esmolol, and adenosine in normal dogs demonstrated the superior efficacy of intravenous diltiazem in slowing AV nodal conduction while maintaining a favorable hemodynamic profile.[9] Esmolol was a significantly less effective negative dromotrope than diltiazem and caused a severe drop in left ventricular contractility measurements at dosages which did prolong AV nodal conduction. Adenosine, even at dosages of 2 mg/kg, was ineffective in slowing canine AV nodal conduction. A similar study has not been performed in cats. Diltiazem is administered at dosages of 0.125 to 0.35 mg/kg slow IV over 2 to 3 minutes.[1,9] A constant rate infusion (CRI) (0.125 to 0.35 mg/kg/hr) can be used if frequent recurrence of the arrhythmia occurs before the onset of efficacious oral antiarrhythmic therapy. Esmolol is an ultrashort-acting β_1-selective blocker that typically is administered at 0.5 mg/kg IV over 1 minute.[1] Its brief half-life compared with that of propranolol makes esmolol the preferred parenteral β-blocker. It should nonetheless be used very cautiously in animals with impaired ventricular systolic function, because it will markedly depress ventricular contractility.

Figure 46-2 Sites of action for various antiarrhythmic drugs, highlighting their utility for specific supraventricular tachyarrhythmias. *AV,* Atrioventricular; *SA,* sinoatrial. From Bonagura JD: *Kirk's current veterinary therapy XIII,* ed 13, Philadelphia, 2000, Saunders.



Other agents can prolong the effective refractory period or slow conduction within the myocardium, including an accessory pathway or atrial myocardium. These agents can terminate both atrial and AV node–dependent tachyarrhythmias. Of these, procainamide is the agent most commonly used in veterinary medicine. A sodium and potassium channel blocker, procainamide decreases abnormal automaticity, slows conduction, and prolongs the effective refractory period in atrial (and ventricular), accessory pathway, and retrograde fast AV nodal tissue. In atrial tachyarrhythmias, other agents are used first to slow AV nodal conduction before administration of procainamide. Parenteral procainamide is administered in dosages of 6 to 8 mg/kg IV over 5 to 10 minutes or 6 to 20 mg/kg IM in dogs. A CRI of 20 to 40 μg/kg/min can be used once a therapeutic response is obtained with bolus administration. Parenteral procainamide in cats is used cautiously at dosages of 1 to 2 mg/kg IV or 3 to 8 mg/kg IM and a CRI of 10 to 20 μg/kg/min.

Direct current (DC) cardioversion or overdrive pacing can be used to terminate certain hemodynamically unstable, sustained SVTs.[10] DC cardioversion in a proper critical care environment with appropriate hemodynamic and electrocardiographic monitoring offers certain distinct advantages over emergency drug therapy. The need to distinguish between supraventricular and ventricular tachyarrhythmias to design appropriate drug therapy is less important when DC cardioversion is employed. Sinus rhythm may be restored immediately with successful DC cardioversion, avoiding the slower titration and potential side effects seen with parenteral drug administration. The need for general anesthesia (albeit brief) is a risk factor for DC cardioversion but should not preclude its use in patients who would benefit from it.

DC cardioversion and overdrive pacing are effective in terminating SVTs caused by reentry rather than abnormal automaticity. Overdrive pacing can be performed without general anesthesia if the patient is depressed or moribund. The jugular furrow can be locally anesthetized with lidocaine, a catheter introducer placed in the external jugular vein, and a multipolar catheter guided fluoroscopically into the right atrium (for intraatrial reentry) or ventricle (more effective for terminating orthodromic AV reciprocating tachycardia). The distal and second poles of this catheter are then attached to a programmable pacemaker. An electrophysiologic recorder (ideal but not necessary) or multilead surface ECG is used to continuously record cardiac electrical activity. Once the myocardium is captured, the pacing rate is increased to 10 to 20 beats/min faster than the tachyarrhythmia rate. One-to-one capture is ensured for a brief period, and then pacing is stopped once intracardiac electrograms confirm termination of the SVT. If only the surface ECG is recorded, pacing is stopped after a brief period to determine if the tachyarrhythmia terminated. If not, a longer period or slightly faster pacing rate is used. Failure to terminate or rapid resumption of the tachyarrhythmia can indicate either an SVT caused by an automatic mechanism or successful termination but then rapid reinitiation of a reentrant SVT.

46.6.2 Long-Term Therapy

46.6.2.1 Medical Treatment

Long-term antiarrhythmic drug therapy must be tailored to each patient based on the type of SVT, the presence or absence of congestive heart failure or structural heart disease, comorbid conditions (particularly hepatic or renal dysfunction, acid-base disturbances, or endocrine diseases that alter the metabolism of specific antiarrhythmic drugs), and concurrent drug administration. Atrial tachyarrhythmias typically are managed by dual antiarrhythmic therapy, one drug to slow AV nodal conduction and a second to terminate the atrial tachyarrhythmia itself. This general rule is violated when persistent atrial fibrillation is present, when rate control becomes the goal. AV node–dependent tachyarrhythmias sometimes will respond to single agent therapy aimed at slowing AV nodal conduction. In reality, however, these tachyarrhythmias often are managed by combination therapy as well. For instance, with orthodromic AV reciprocating tachycardia, one agent is used to slow AV nodal conduction and a second agent is used to block conduction or prolong the effective refractory period within an accessory pathway.

Drugs that slow AV nodal conduction include the classes that were discussed under emergency therapy. The three major classes include: digitalis glycosides, calcium channel blockers, and β-blockers. Animals with systolic dysfunction classically are placed on digoxin as a first-line negative dromotrope (0.005 to 0.01 mg/kg PO q12h in a normokalemic dog with normal renal function; 0.0312 mg PO q24-48h in a normokalemic cat with normal renal function).

The ventricular rate is almost never slowed adequately with digoxin as a single agent, however, and other drugs must be added. The calcium channel blocker diltiazem is effective in prolonging the effective and functional refractory periods of the AV node. This effect is most notable at faster stimulation rates (use dependence) and in depolarized fibers (voltage dependence).[10] Diltiazem has gained preference over verapamil because of its more favorable hemodynamic profile (i.e., minimal negative inotropic effect) at effective antiarrhythmic dosages. Diltiazem is administered 3 times a day, which can be difficult particularly for cat owners. Sustained release preparations, however, appear to have more variable absorption in companion animals, with resultant poorer arrhythmia control. Such preparations also have had a high incidence of side effects in cats, including vomiting, inappetence, and hepatopathies.[9]

Atenolol is a relatively β_1-selective blocker that competitively inhibits the effects of catecholamines on cardiac β-receptors. Thus, underlying sympathetic tone plays an important role in determining the effectiveness of atenolol in prolonging AV nodal conduction and refractoriness or suppressing abnormal atrial foci.[9,10] Because of its negative inotropic effects, the dosages required to affect AV nodal conduction significantly are often not well tolerated by animals with left ventricular (LV) systolic dysfunction. The beneficial effects of β-adrenergic blockade in the face of impaired LV systolic function have been well demonstrated in human patients; therapy must begin at very low dosages and up-titration performed very slowly.[11] Patients with rapid SVTs do not have the luxury of this prolonged time for control of their ventricular rate. Remember that the rapid ventricular rate is worsening or may be the sole cause for their myocardial dysfunction. Atenolol is particularly useful in cats with hypertrophic cardiomyopathy and SVTs. Because of its renal clearance, the dosage of atenolol must be decreased in the face of concurrent renal disease.

Class I antiarrhythmic drugs block fast sodium channels and thus suppress abnormal automaticity and slow myocardial conduction velocity. The most commonly used class I drug in small animals with SVT is procainamide, a class Ia drug that also prolongs repolarization through its potassium channel blocking capabilities. Oral procainamide typically is used as an extended release preparation, administered 10 to 30 mg/kg PO q8h in dogs and 3 to 8 mg/kg PO q8h in cats. Poor absorption of sustained release procainamide preparations can limit their effectiveness in certain animals. The need for 2-hour to 6-hour dosing of formulations that are not extended release makes compliance nearly impossible. GI side effects can be prominent, and proarrhythmia is a definite concern with long-term procainamide therapy.

Class III antiarrhythmic agents are used to prolong the effective refractory period of atrial myocardium and accessory pathways. Sotalol and amiodarone, the two agents used in small animals, have additional antiarrhythmic actions, including slowing of AV nodal conduction. Sotalol typically is administered at 1 to 2 mg/kg PO q8h for SVTs, but amiodarone dosing varies and typically includes a loading period.[9] The author uses 15 mg/kg q24h for 7 days, then 10 mg/kg q24h for 7 days, then 5 mg/kg q24h for maintenance. Serum amiodarone levels can be measured but may not correlate with tissue concentrations. The high incidence of reported side effects in dogs receiving long-term amiodarone therapy has limited its widespread use.[9,12] Amiodarone has not been used in cats.

46.6.2.2 Catheter Ablation

Certain SVTs can be cured, rather than simply controlled, with transvenous radiofrequency catheter ablation.[6,13] The tachyarrhythmia circuit is first mapped with numerous multielectrode catheters. Once, for example, an accessory pathway is identified, detailed mapping is used to locate precisely the pathway along the AV groove. A specialized catheter with a 4-mm to 5-mm distal electrode is positioned at this critical site, and radiofrequency energy is delivered to the tip electrode causing thermal dessication of a small volume of tissue, to permanently interrupt the tachycardia circuit. This technique has been used by this author and others in a number of canine cases.

46.7 SUGGESTED FURTHER READING*

NS Moise: Electrocardiography and cardiac arrhythmias. In S Ettinger, B Feldman (Eds.): *Textbook of veterinary medicine*. ed 6, 2005, Saunders, St Louis, *An excellent review chapter of the basic ECG, arrhythmias, and antiarrhythmic drugs for the small animal clinician*.

KN Wright: Assessment and treatment of supraventricular tachyarrhythmias. In JD Bonagura (Ed.): *Kirk's current veterinary therapy XIII*. ed 13, 2000, Saunders, St Louis, *A good, brief overview of supraventricular tachyarrhythmias in companion animals*.

KN Wright: Interventional catheterization for tachyarrhythmias. In JA Abbott (Ed.): *Veterinary clinics of North America: small animal practice*. 2004, Saunders, Philadelphia, *An excellent review of the progress made in the field of catheter ablation therapy to cure certain tachyarrhythmias in dogs*.

* See the CD-ROM for a complete list of references.

47 Chapter 47 Ventricular Tachyarrhythmias

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47.1 KEY POINTS

- Wide QRS complex tachycardia with atrioventricular dissociation, fusion beats, and capture beats are electrocardiographic features diagnostic of ventricular tachycardia (VT).
- Clinical signs secondary to VT are determined by its rate and duration.
- The most common noncardiac causes of VT are hypoxemia, electrolyte imbalances (hypokalemia), acid-base disorders, and drugs.
- The most common cardiac diseases associated with clinical VT are Boxer cardiomyopathy and dilated cardiomyopathy in Doberman Pinschers.
- Antiarrhythmic medications do not prevent sudden death.
- Antiarrhythmic therapy is initiated if clinical signs associated with VT are present.
- When the origin (supraventricular or ventricular) of a wide QRS tachycardia cannot be determined, it must be managed as if it were VT.
- Lidocaine is the first-choice parenteral antiarrhythmic drug for treatment of VT in dogs.

47.2 INTRODUCTION

Physiologically, specialized ventricular cells, known as *Purkinje fibers,* may work as a pacemaker when the sinus and atrioventricular nodes fail to function appropriately, resulting in a ventricular escape rhythm or idioventricular rhythm at a rate of about 30 to 40 beats/min in dogs and 60 to 130 beats/min in cats.[1,2] Three arrhythmogenic mechanisms known as *enhanced automaticity, triggered activity, and reentry* (Box 47-1) may affect Purkinje cells or any excitable ventricular myocyte and result in ventricular tachycardia (VT).[3] They result in a ventricular rhythm faster than the physiologic idioventricular rhythm. Most human cardiologists define VT as three or more consecutive ventricular beats occurring at a rate faster than 100 beats/min, the conventional upper limit for normal sinus rhythm. In our patients, normal sinus rhythm can probably reach 150 to 180 beats/min in dogs and 220 beats/min in cats. These rates define the lower limit for VT. If a ventricular rhythm is faster than the physiologic idioventricular rhythm and slower than VT, it is called *accelerated idioventricular rhythm (AIVR)*. The rate of an AIVR is within the range of the underlying sinus rhythm. Therefore both rhythms are seen competing on a surface electrocardiogram (ECG) because the faster pacemaker inhibits the slower one, a property known as *overdrive suppression*. [2] Besides rate, an important feature of VT is duration, because both determine the clinical consequences of the arrhythmia. VT is described as nonsustained if it lasts less than 30 seconds and sustained if it lasts longer.

47.2.1

Box 47-1 Electrophysiologic Mechanismsof Ventricular Tachycardia

Reentry: Requires an impulse to leave a point of departure and return to its starting point with a sufficient delay that the cardiac tissue has recovered its excitability. It usually circles around an area of nonconductive tissue (fibrosis, vessel). Shortening of the refractory period and slow conduction favor this self-perpetuating mechanism.

Enhanced automaticity: A myocardial cell that never possessed the property of automaticity while healthy gets the ability to depolarize spontaneously when depressed. Its membrane potential is less negative, and the action potential becomes similar to that of the sinus node.

Triggered activity: Results from small membrane depolarizations that appear after and are dependent on the upstroke of the action potential. They trigger an action potential when they reach the threshold potential. When they occur during the process of repolarization they are called *early afterdepolarizations (EADs),* and when they occur after full repolarization they are called *delayed afterdepolarizations (DADs)*. Hypokalemia and drug-induced prolongation of the QT segment increase the risk of EADs. DADs occur secondary to intracellular calcium overload associated with sustained tachycardia and digoxin toxicity.

47.3

ELECTROCARDIOGRAPHIC DIAGNOSIS

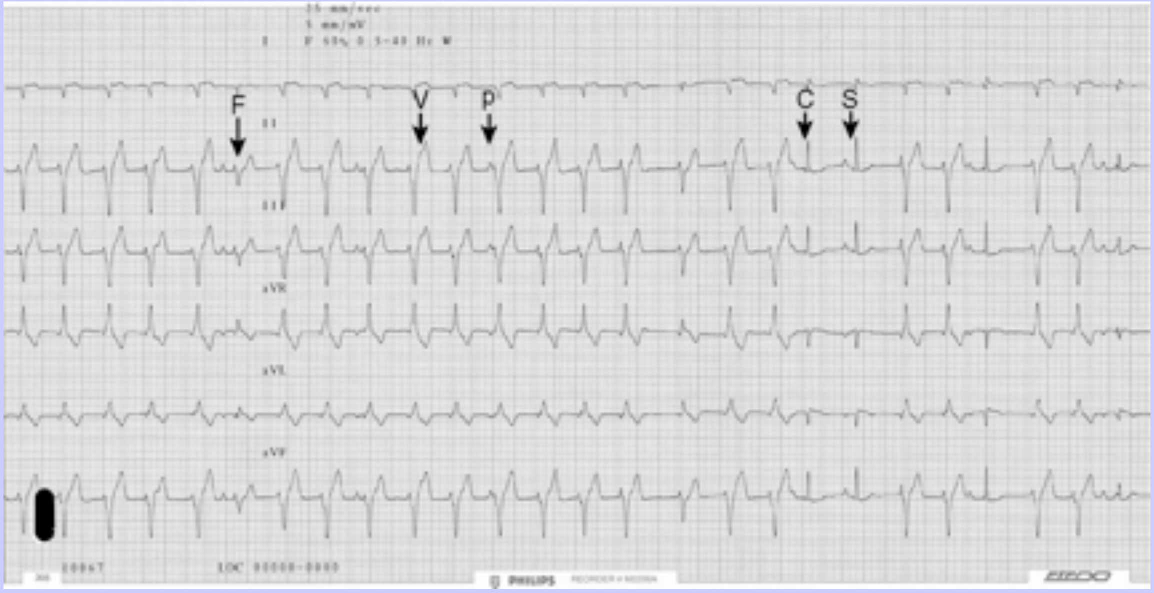
In the intensive care unit, VT is first suspected on physical examination or detected on a continuous ECG monitor. Confirmation of VT relies on a good-quality 6-lead to 12-lead surface ECG recording with the patient placed in right lateral recumbency.

Ventricular tachycardia is identified as a broad QRS tachycardia with complexes wider than 0.06 second in dogs and 0.04 second in cats. Each QRS complex is followed by a large T wave, directed opposite to the QRS deflection.

The challenge of ECG interpretation is to differentiate VT from supraventricular tachycardias (SVTs) with broad QRS complexes because of aberrant conduction of the electrical impulse within the ventricles. Aberrant ventricular conduction results from a structural bundle branch block, a functional or rate-related bundle branch block, or finally an accessory atrioventricular pathway causing preexcitation.[4]

The three most reliable diagnostic criteria of VT are atrioventricular dissociation, fusion beats, and capture beats (Figure 47-1). Atrioventricular dissociation is demonstrated when P waves are occasionally seen on the ECG tracing but are not related to ventricular complexes. These P waves reflect atrial activity independently from the ventricle. 200 201 On occasion apparent atrioventricular association may be seen, or ventricular beats can conduct in a retrograde fashion to the atrium in a 1:1 ratio. Therefore signs of atrioventricular association do not rule out VT. Fusion beats and capture beats are seen with paroxysmal VT and AIVR. Fusion beats result from the summation of a ventricular impulse and a simultaneous supraventricular impulse resulting in a QRS complex of intermediate morphology and preceded by a P wave (unless there is concurrent atrial fibrillation). A capture beat is a supraventricular impulse conducting through the normal conduction pathways to the ventricle during an episode of VT or AIVR. This complex occurs earlier than expected and is narrow if the conduction system is intact.[4]

Figure 47-1 Electrocardiographic recording from a dog; paper speed is 25 mm/sec. There is ventricular tachycardia *(V)* at a rate of 150 beats/min. P waves *(p)* not related to the wide QRS complexes *(V)* indicate atrioventricular (AV) dissociation. There are fusion beats *(F)* with an intermediate morphology and capture beats *(C)*. Note that the PR interval of the capture beat is prolonged compared with a normal sinus beat *(S)*. It results from retrograde depolarization of the AV node by the preceding ventricular impulse and secondary slowing of the propagation of the sinus impulse in a partially refractory node, a phenomenon known as *concealed AV conduction*.



Regularity of the rhythm is a less accurate criterion because VT can be slightly irregular. When the RR interval varies by 100 msec or more, it is suggestive of atrial fibrillation with aberrant ventricular conduction. Other criteria have been suggested by human cardiologists to make the correct diagnosis; for example, QRS complexes are usually wider with VT than with SVT.[4] Although rarely effective, vagal maneuvers can be done to slow the atrioventricular conduction, revealing P waves associated to the QRS complexes in case of SVT. It is also important to consider the overall clinical picture. For example, Boxers and Doberman Pinschers usually have VT. Finally, it is accepted that managing SVT as VT is usually less dangerous than the opposite, because drugs used to stop SVT or to slow the ventricular response rate to rapid atrial impulses (i.e., calcium channel blockers and β-blockers) do not interrupt VT and worsen hypotension with their vasodilatory or negative inotropic effects.

If doubt persists, treat as if it were VT.

47.4 APPROACH TO THE PATIENT WITH VENTRICULAR TACHYCARDIA

Once VT is confirmed on a surface ECG, the possible causes for the initiation and maintenance of the arrhythmia must be identified. The knowledge will help planning an effective treatment protocol and predicting the short-term and long-term prognoses. It is useful to differentiate cardiac from noncardiac causes of VT.

47.4.1 Noncardiac Causes Of Ventricular Tachycardia

Ventricular cells are sensitive to hypoxemia, electrolyte and acid-base imbalances, sympathetic stimulation, and various drugs. These changes typically affect the passive and energy-dependent ion exchanges across the cellular membrane of the myocyte during the initiation and propagation of the action potential.

Hypokalemia is the most commonly reported electrolyte disturbance responsible for or contributing to VT. It increases phase 4 depolarization, increasing spontaneous automaticity, and prolongs the action potential duration, which promotes arrhythmias from triggered activity.[5] Because digoxin competes with potassium on its receptors, hypokalemia increases the risk of digoxin toxicity. Similar arrhythmias result from hypomagnesemia, because magnesium is necessary for proper functioning of the sodium-potassium ATP pump, which maintains normal intracellular potassium concentration. Hypocalcemia and hypercalcemia are also responsible for ventricular arrhythmias.

Increased adrenergic tone potentiates arrhythmias through various mechanisms. In the intensive care unit, drugs with sympathetic or sympatholytic activity are used commonly and should be stopped when possible to assess their role in the perpetuation of VT.

It is also important to evaluate the potential proarrhythmic effects of all the medications given to a patient with VT. There are many publications on drug-induced prolongation of the QT segment. Prolongation of the QT segment reflects prolongation of the cardiac cell membrane repolarization and indicates a risk of ventricular arrhythmia from triggered activity. Antiarrhythmic drugs, such as procainamide and sotalol, but also domperidone, cisapride, chlorpromazine, and erythromycin, are known to prolong the QT segment. Bradycardia and hypokalemia contribute to this effect on repolarization and increase the risk of VT.[6]

Oxygen therapy, identification and correction of all electrolyte disturbances, and discontinuation of proarrhythmic medications are the initial and necessary first steps in the treatment of all patients with VT.

47.4.2 Cardiac Causes of Ventricular Tachycardia

In most patients with VT an echocardiogram is indicated as soon as possible to identify an underlying cardiac disease as the cause for the arrhythmia. In humans the association of sustained VT and heart failure is a marker of increased risk of sudden death from arrhythmia, and this is probably true in our patients as well.[7] Identification of cardiac disease may help to elaborate an effective treatment strategy, to know what to expect from the intervention, and to give the most accurate prognosis to the owner. Today there is valuable information on some breed-specific VTs.

VT is on occasion observed in patients with cardiac tumors (with or without associated tamponade), myocarditis, endocarditis, and acute coronary events associated with hypothyroidism.

VT is an important part of the clinical picture of dilated cardiomyopathy in some breeds. The prevalence of ventricular arrhythmias was 21% in a pool of breeds with dilated cardiomyopathy, 16% in Newfoundlands and 92% in Doberman Pinschers. The natural history of the disease has been studied extensively in Doberman Pinschers. There is an occult stage of the disease with no clinical signs but with echocardiographic indicators of left ventricular dysfunction and a risk of sudden death of approximately 30%. It can last 2 to 4 years. In the overt stage of the disease, congestive heart failure is present and the risk of sudden death is about 30% to 50%. In Doberman Pinschers, most ventricular ectopies have a right bundle branch block morphology in lead II of the surface ECG, indicating their origin in the left ventricle.[8]

Cardiomyopathy of Boxers is known as *arrhythmogenic right ventricular cardiomyopathy (ARVC)*. It is an adult-onset disease with a concealed form characterized by occasional ventricular ectopies only, followed by an overt form with VT associated with exercise intolerance and collapse. On occasion myocardial failure is observed. In ARVC, ventricular ectopies typically have a left bundle branch block morphology, indicating their right-sided origin.[9]

An inherited ventricular arrhythmia has been identified in some German Shepherds. In the most severe form of the disease these dogs have a propensity for sudden death until 18 months of age. The form of VT responsible for sudden death is polymorphic, rapid (more than 300 beats/min), nonsustained, and usually preceded by a pause.[10]

Dogs with severe subaortic stenosis and pulmonic stenosis are prone to syncope and sudden death. VT progressing to ventricular fibrillation may contribute to some of these episodes.

In cats, VT may be seen in association with idiopathic hypertrophic cardiomyopathy and with concentric hypertrophy secondary to hypertension and hyperthyroidism.

47.5 ANTIARRHYTHMIC TREATMENT

47.5.1 Decision to Treat

Antiarrhythmic agents are indicated to treat symptomatic VT and prevent its recurrence. Despite many large-scale randomized studies in humans and a few publications in veterinary medicine, there is no indication that antiarrhythmic agents can prevent sudden death, and on some occasions they may precipitate it.[7]

Hemodynamic compromise usually is associated with rapid (more than 200 beats/min) and sustained VT in a patient with concurrent cardiac disease. Slower nonsustained VT and AIVR are usually auscultatory or ECG findings in patients with motor vehicle–related trauma, gastric dilatation-volvulus, or metabolic imbalances and resolve spontaneously, with no antiarrhythmic medications within 4 days.[11]

Some ECG characteristics of VT are viewed as indicators of an increased risk for sudden death and may influence the decision of the clinician toward treatment. Hemodynamic collapse is more likely to result from polymorphic VT, which is characterized by a continuously changing QRS complex pattern, than monomorphic VT. Antiarrhythmic agents are generally considered for sustained VT with rates greater than 180 to 200 beats/min. The presence of polymorphic VT may encourage treatment at the lower rate range. “R-on-T phenomenon” describes the superimposition of an ectopic beat on the T wave of the preceding beat. Some observations suggest that it may represent an increased risk for VT and sudden death from ventricular fibrillation. Nevertheless strong evidence is lacking and this finding by itself cannot justify treatment.

Regardless of its cause, rate, duration, or morphology, the decision to treat VT with antiarrhythmic medications must be dictated primarily by the clinical signs related to it.

47.5.2 Antiarrhythmic Drugs

A few antiarrhythmic agents will manage most VTs. Because studies in veterinary medicine are lacking and antiarrhythmic medications are complex drugs with many side effects including proarrhythmic effects, it is important to gain experience with only a few commonly used drugs.

47.5.2.1 Lidocaine

Lidocaine is the first-choice intravenous agent to control VT. It works better on rapid VTs and in normokalemic animals. In dogs boluses of 1 to 2 mg/kg can be repeated every 10 to 15 minutes. A maximum dose of 8 mg/kg/hr is recommended to avoid neurotoxic effects. The arrhythmia can be controlled over time with a continuous infusion of lidocaine at a rate between 25 and 80 μg/kg/min. In cats, the safety margin is smaller and lower dosages of lidocaine can be used, but β-blockers usually are preferred. Mexiletine has properties similar to those of lidocaine and is available as an oral medication. Mexiletine, 4 to 8 mg/kg q8h, combined with atenolol, 0.5 mg/kg q12-24h, has been shown to control VT in Boxers with ARVC.[9,12]

47.5.2.2 Procainamide

Procainamide is used intravenously for VTs that do not respond to lidocaine. A bolus of 10 to 15 mg/kg over 1 to 2 minutes can be followed by a constant rate infusion at 25 to 50 μg/kg/min. Rapid intravenous injection can cause hypotension. Long-term management of VT can be attempted with oral procainamide at 10 to 20 mg/kg q6h, or q8h if the sustained-release form is used.[12]

47.5.2.3 β-Blockers

Sympathetic activation has been implicated in the pathogenesis of ventricular arrhythmia. β-Blockers provide adrenergic system blockade and may help control arrhythmias. 202 203 Esmolol is a short-acting β-blocker that can help control sympathetically driven VTs such as those associated with pheochromocytoma or thyrotoxic disease in cats, but its negative inotropic effects may be too pronounced in some patients and cause cardiovascular collapse.

47.5.2.4 Sotalol

Sotalol is an oral medication usually effective in controlling VT. It was the second most effective treatment protocol after a combination of mexiletine and atenolol in Boxers with ARVC. In Boxers, sotalol usually is given at 2 mg/kg q12h.[9,12]

47.6 POSTINTERVENTION MONITORING

Because the response to antiarrhythmic agents cannot be predicted, continuous ECG monitoring is essential after the medication is started and for a minimum of 24 hours. It will give valuable information on the control of the arrhythmia and the possible proarrhythmic effects of the drugs. Twenty-four hour Holter recording is more adapted to long-term management of the arrhythmia.

47.7 SUGGESTED FURTHER READING*

MD Kittleson: Diagnosis and treatment of arrhythmias (dysrhythmias). In MD Kittleson, RD Kienle (Eds.): *Small animal cardiovascular medicine*. 1999, Mosby, St Louis, *Complete review of supraventricular and ventricular arrhythmias featuring many ECG tracings*.

KM Meurs: Boxer cardiomyopathy: an update. In JA Abbott (Ed.): *Veterinary Clinics of North America current issues in cardiology*. 2004, Saunders, Philadelphia, *Excellent review on Boxer cardiomyopathy. Presents the studies that led to the reclassification of the disease as arrhythmogenic right ventricular dysplasia*.

NS Moise: Diagnosis and management of canine arrhythmias. In RP Fox, D Sisson, NS Moise (Eds.): *Textbook of canine and feline cardiology. Principles and clinical practice*. 1988, Saunders, Philadelphia, *Describes the mechanisms of action and use of antiarrhythmic drugs. Details their effects at the cellular level*.

MR O'Grady, ML O'Sullivan: Dilated cardiomyopathy: an update. In JA Abbott (Ed.): *Veterinary Clinics of North America current issues in cardiology*. 2004, Saunders, Philadelphia, *Review of dilated cardiomyopathy in dogs with emphasis on Doberman cardiomyopathy*.

HJL Marriott, M Boudreau Conover: Arrhythmogenic mechanisms and their Modulation. In HJL Marriott, M Boudreau Conover (Eds.): *Review of the electrophysiologic mechanisms of arrhythmia: advanced concepts in arrhythmias*. ed 3, 1998, Mosby, St Louis.

* See the CD-ROM for a complete list of references.

48 Chapter 48 Myocarditis

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48.1 KEY POINTS

- Myocarditis is an inflammatory process involving the heart. Inflammation may involve the myocytes, interstitium, or vascular tree.
- Myocarditis has been associated with a wide variety of diseases. Infectious agents (viral, bacterial, protozoal) may cause myocardial damage by myocardial invasion, production of myocardial toxins, or activation of immune-mediated disease.
- Myocarditis can also be associated with physical agents (doxorubicin), underlying metabolic disorders (uremia), toxins (heavy metals), or physical agents (heat stroke).

48.2 INTRODUCTION

Myocarditis is a rare cause of heart failure in dogs and extremely rare in cats. Clinical pictures vary, including asymptomatic patients who may have electrocardiographic abnormalities and patients with or without heart enlargement, systolic dysfunction, or even full-blown congestive heart failure. The patient's history (i.e., environment and exposure) is often critical in determining likely risk and suggesting appropriate diagnostic tests. Clinical reports of canine myocarditis are most common in immunocompromised or immunonaïve patients.

48.3 INFECTIOUS MYOCARDITIS

48.3.1 Viral Myocarditis

Numerous viruses have been associated with myocarditis in humans. In dogs, viral myocarditis appears most commonly in immunonaïve patients, and the virus most commonly associated with the disease is parvovirus. However, at this time the entity appears to be very rare. In the late 1970s and early 1980s, when the parvovirus pandemic first was recognized, puppies did not receive maternal antibodies and very young puppies developed a fulminant infection with acute death due to pulmonary edema when exposed to the virus. Older puppies (2 to 4 months) often died subacutely from congestive heart failure, but others developed a milder myocarditis and later developed dilated cardiomyopathy (DCM), usually as young adults. Basophilic intranuclear inclusion bodies are found in the myocardium of acutely affected younger puppies, but may be absent in older puppies.[1] 204 Older dogs typically have gross myocardial scarring. Rare cases of parvovirus-induced myocarditis have been reported since the early to mid-1980s.

Rarely, other viruses have been associated with myocarditis in dogs. In 2001, Maxson and others evaluated myocardial tissue from 18 dogs with an antemortem diagnosis of DCM and 9 dogs with a histopathologic diagnosis of myocarditis based on a polymerase chain reaction analysis to screen for canine parvovirus, adenovirus types 1 and 2, and herpesvirus. Canine adenovirus type 1 was amplified from myocardium of only one dog with DCM and none of the dogs with myocarditis, suggesting these pathogens are not commonly associated with DCM or active myocarditis in the dog.[2] Distemper virus–associated cardiomyopathy with a mild inflammatory infiltrate has been produced by experimental infection of immunonaive puppies.[3] Natural infection with West Nile virus was associated with myocarditis in a wolf and a dog in 2002, the third season of the West Nile virus epidemic in the United States.[4] Viral genomic deoxyribonucleic acid has also been identified in feline myocardial tissue from patients with hypertrophic cardiomyopathy, DCM, and restrictive cardiomyopathy, suggesting that viral myocarditis may be a factor in these feline-acquired diseases.[1]

48.3.2 Protozoal Myocarditis

48.3.2.1 Chagas Disease

Chagas disease is caused by *Trypanosoma cruzi,* a protozoal parasite. Chagas disease is the leading cause of DCM in humans of Latin America, but it is rare in North America. In North American dogs, Chagas disease occurs most commonly in Texas and Louisiana. There have been no reported feline cases in North America. The organism is transmitted by an insect vector (Reduviidae), and reservoir hosts include rodents, raccoons, opossums, dogs, cats, and humans. The trypomastigote is the infective stage, but on entering host cells the organism enters the reproductive stage and becomes an amastigote. Amastigotes multiply until the host cell ruptures.[1,8]

Dogs with clinical Chagas disease have an acute or a chronic syndrome. In the acute stage, circulating trypomastigotes may be seen in a thick blood smear, and most dogs are brought for treatment because of sudden development of signs of right-sided heart failure (ascites, tachycardia, lethargy). Dogs with chronic Chagas disease may enter a quiescent stage free of clinical signs for months or even years. Nervous system damage often causes ataxia and weakness in these patients.[1,8]

48.3.3 Bacterial and Other Causes of Myocarditis

Bacterial myocarditis is possible whenever bacteremia or sepsis is present, with the most common agents being staphylococcal and streptococcal species.[1] Myocarditis associated with *Citrobacter koseri,* an opportunistic pathogen of immunosuppressed human patients, has been described in two 12-week-old sibling Boxer puppies.[5] Tyzzer disease (infection with *Bacillus piriformis*) was associated with severe necrotizing myocarditis in a wolf-dog hybrid puppy.[6]

Myocarditis has also been recognized secondary to rickettsial organisms such as *Rickettsia rickettsii, Ehrlichia canis,* and various *Bartonella* species.[1] Myocarditis has been noted in 2 of 12 dogs diagnosed with endocarditis, 11 of which were seroreactive to *Bartonella vinsonii* subspecies.[7] Lyme disease (secondary to infection by the spirochete *Borrelia burgdorferi*) has been implicated as a cause of myocarditis in dogs, but documented cases are rare. Clinical signs are often vague and nonspecific, and serologic testing is not a reliable method to determine active infection.[1] In humans, Lyme myocarditis may be due to direct toxic effects or immune-mediated mechanisms, and the disease is usually self-limiting.[11] Fungal infections of the myocardium are extremely rare but have occurred in immunocompromised patients.[1]

A group of cats was described with transient fever and depression that appeared to be infectious in nature. Postmortem examination revealed microscopic lesions consistent with myonecrosis and an inflammatory cell infiltrate. A viral etiology was suspected, but no organism was identified.[8] In a retrospective study reviewing

1472 feline necropsies over a 7-year period, 37 cases were diagnosed with endomyocarditis. The cats with endomyocarditis had a mean age at death of 3.4 years, and 62% of them had a history of a stressful event 5 to 10 days before being brought for treatment. Interstitial pneumonia was present in 77% of the cats at postmortem examination. Special stains for bacteria and fungi were negative.[9]

Parasitic agents can also lead to myocarditis. *Toxoplasma gondii* bradyzoites can encyst in the myocardium, resulting in chronic infection. Eventually the cysts rupture, leading to myocardial necrosis and hypersensitivity reactions.[1] *Neospora caninum* can infect multiple tissues, including the heart, peripheral muscles, and central nervous system. Clinical signs associated with noncardiac tissues typically predominate; however, collapse and sudden death has been reported in affected dogs.[1] Infestation with *Trichinella spiralis* is a common cause of mild myocarditis in humans.[11] The parasite has been associated with at least one case of canine myocarditis complicated by arrhythmias (Figure 48-1).[12]

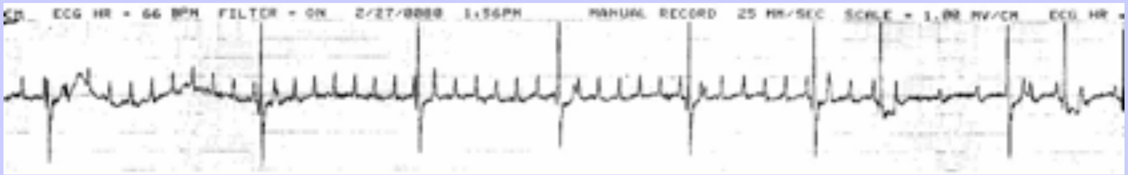
48.4 NONINFECTIOUS MYOCARDITIS

48.4.1 Doxorubicin Toxicity

Doxorubicin cardiotoxicity may be manifested as arrhythmias, myocardial failure, or both. Cardiotoxicity is dosage-dependent and irreversible and is more common at cumulative doses exceeding 250 mg/m^2; however, in one study in which only two doses of 30 mg/m^2 were administered, 3% of dogs developed cardiomyopathy.[1,8] The time to onset of CHF in affected dogs is highly variable. Although pathologic changes have been seen in the feline myocardium following administration, no antemortem echocardiographic or electrocardiographic changes associated with doxorubicin toxicity have been reported.

Other causes of noninfectious myocarditis, although rarely recognized in veterinary medicine, include allergic reactions, systemic diseases such as vasculitis, or physical agents such as radiation or heat stroke.[11] Numerous chemicals and drugs may lead to cardiac damage and dysfunction. A severe reversible DCM has been observed in humans with pheochromocytoma,[11] and similar findings have been observed in experimental animals receiving prolonged infusions of norepinephrine.[11] Myocardial coagulative necrosis was found in a dog that died suddenly after an episode of severe aggression, restraint, and sedation for grooming.[13] Myocardial lesions were presumed to be caused by catecholamine toxicity.

Figure 48-1 Electrocardiogram from a mixed-breed dog with trichinosis involving the heart. The dog was brought in for collapse due to complex arrhythmias. Note the ventricular escape beats. An underlying supraventricular tachycardia is likely as well.


ECG HR = 66 BPM FILTER = ON 2/27/0000 1:56PM MANUAL RECORD 25 MM/SEC SCALE = 1.00 MV/CM ECG HR

48.5 DIAGNOSIS

Definitive diagnosis, unless the history clearly suggests myocarditis (e.g., doxorubicin toxicity) is elusive (Box 48-1). Supportive clinical laboratory tests include leukocytosis or eosinophilia, particularly in parasitic or allergic myocarditis. Elevated cardiac troponin I levels provide evidence of myocardial cell damage in patients suspected of having myocarditis. If a high suspicion for Chagas disease is present, serologic examination for *T. cruzi* is diagnostic. Demonstration of a rising titer is also helpful to establish the diagnosis of myocarditis associated with *T. gondii* or *N. caninum*. Viral and rickettsial testing should be performed if indicated. Blood cultures should be performed if a bacterial cause is suspected. Thoracic radiographs may show normal heart size or heart enlargement with or without evidence of CHF. The electrocardiographic findings may also be varied, and ventricular arrhythmias or conduction disturbances are common. Echocardiography most often demonstrates systolic dysfunction, either global or regional, and cardiac chambers may be normal or increased in size.

Endomyocardial biopsy (the gold standard for diagnosis of myocarditis in humans[10]) may allow definitive antemortem diagnosis (Color Plate 48-1). However, a focal myocarditis can still be missed because the sample size is small. At postmortem examination, immunohistochemistry or electron microscopy can confirm the diagnosis of *N. caninum* infection.[9] Gross pathology findings may be insignificant, or they may reveal cardiac dilation or ventricular hypertrophy, focal petechiae, and myocardial abscesses.[1] Specific findings depend on the underlying etiology. Focal or diffuse myocarditis is definitively diagnosed by histopathology when myocyte necrosis, degeneration, or both are associated with an inflammatory infiltrate.[1]

48.6 TREATMENT

Most recommendations for managing myocarditis in dogs and cats are extrapolated from human medicine or research with models of viral myocarditis. Supportive care is the first line of therapy for patients with myocarditis. In those patients with signs of CHF, typical therapy should include preload reduction with diuretics and afterload reduction with angiotensin-converting enzyme inhibitors (see Chapter 21, Pulmonary Edema). Digoxin increased expression of proinflammatory cytokines and increased mortality in experimental myocarditis, so it is recommended to be used with caution and at low dosages.[10] Intravenous inotropic therapy in the form of dobutamine can be useful if significant systolic dysfunction is present.

Eliminating unnecessary medications may help reduce the possibility of allergic myocarditis. Results of recent studies suggest that immunosuppression is not routinely helpful in myocarditis patients, but it may have an important role in patients with myocardial dysfunction caused by systemic autoimmune disease.[10] Nonsteroidal antiinflammatory agents are contraindicated during the acute phase of myocarditis in humans (during the first 2 weeks), because they increase myocardial damage. However, they appear to be safe later in the course of disease.[11] In a murine model of viral myocarditis, angiotensin-converting enzyme inhibition (with captopril) was beneficial. Similarly, interferon therapy is beneficial in the experimental model of myocarditis and may be useful clinically.[11]

48.6.1 Box 48-1 Characteristics Suggestive of Myocarditis

- History suggests it is possible (e.g., oncology patient receiving doxorubicin, dog lives in Texas)
- Unusual signalment for heart disease (e.g., Irish Setter, German Shepherd)

- Supportive electrocardiographic findings that include conduction abnormalities or arrhythmias
- Supportive echocardiographic findings that include myocardial dysfunction (which may be regional) with or without heart enlargement
- Supportive clinical laboratory findings that include leukocytosis, eosinophilia, elevated cardiac troponin I levels

When diagnosis of acute Chagas disease is possible, several agents appear to inhibit *T. cruzi;* however, by the time a diagnosis is made it is often too late for this approach. Patients with chronic Chagas disease are treated symptomatically for CHF. Similarly, successful treatment has been reported using several agents in dogs affected with *N. caninum* myocarditis, but severely ill dogs often die.[1] Clindamycin is the drug of choice for treating clinical toxoplasmosis in dogs and cats; however, significant damage to the heart is irreversible.[14]

Dogs with evidence of bacteremia should be treated with antibiotics pending culture and sensitivity results. Empiric treatment should be effective against staphylococcal and streptococcal species (see Chapter 108, Gram-Positive Infections). Animals with suspected rickettsial disease should be treated with doxycycline (5 mg/kg PO or IV q12h) pending titer results.

48.7 SUGGESTED FURTHER READING*

JP Dubey, MR Lappin: Toxoplasmosis and neosporosis. In CE Green (Ed.): *Infectious diseases of the dog and cat*. ed 3, 2006, Saunders, St Louis, *Excellent and detailed chapter on these parasitic diseases*.

PR Fox, D Sisson, NS Moise: In *Textbook of canine and feline cardiology*. ed 2, 1999, Saunders, Philadelphia, *Excellent and detailed general small animal cardiology text with several sections of relevance to this topic*.

MD Kittleson: Primary myocardial disease leading to chronic myocardial failure (dilated cardiomyopathy and related diseases). In MD Kittleson, RD Kienle (Eds.): *Small animal cardiovascular medicine*. 1999, Mosby, Philadelphia, *Excellent general and detailed text on small animal cardiology, one chapter in particular focusing on this topic*. 205 206

TR Maxson, KM Meurs, LB Lehmkuhl, et al.: Polymerase chain reaction analysis for viruses in paraffin-embedded myocardium from dogs with dilated cardiomyopathy or myocarditis. *Am J Vet Res*. **62**, 2001, 130, *Study using polymerase chain reaction technology to screen myocardial specimens from 18 dogs (with an antemortem diagnosis of DCM) and 9 dogs (with a histopathologic diagnosis of myocarditis) for various viral genomes*.

* See the CD-ROM for a complete list of references

49 Chapter 49 Arterial Catheterization

Elisa M. Mazzaferro, MS, DVM, PhD, DACVECC

49.1 KEY POINTS

- Arterial catheters can be placed in the dorsopedal, radial, femoral, coccygeal, and auricular arteries.
- Arterial catheters can be used for direct blood pressure monitoring and procurement of arterial blood samples for blood gas and other analyses.
- Arterial catheters are generally well tolerated, but they can become dislodged easily with excessive patient movement.
- Arterial catheters should be avoided in patients with severe coagulation abnormalities whenever possible because of the risk of arterial hemorrhage.
- Arterial catheters are not well tolerated in cats and should be kept in place no longer than 6 to 8 hours.
- All arterial catheters should be labeled “Arterial Catheter—Not for IV Infusion” to prevent inadvertent injection of fluids or drugs into the arterial line.

49.2 INTRODUCTION AND INDICATIONS FOR ARTERIAL CATHETERIZATION

An indwelling arterial catheter is a necessary and useful procedure for many critically ill veterinary patients. Arterial catheters can be used to collect arterial blood samples when measuring an animal's arterial oxygenation and ventilation and for invasive direct arterial blood pressure monitoring. To avoid complications associated with hemorrhage or arterial thrombosis, the animal's coagulation status should be checked before considering placement of a catheter in any artery. Ideally, a platelet count or estimate, activated partial thromboplastin time, and prothrombin time should be evaluated before catheter placement. If severe thrombocytopenia (<50,000 platelets/µl) or prolonged activated partial thromboplastin time and prothrombin time are present, the patient may be at risk for hemorrhage from the site of arterial catheterization.

Arterial catheters are placed most frequently in the dorsopedal artery.[1] This location is technically the simplest, and it enables easy hemostasis. Alternative locations for arterial catheter placement include the auricular artery on the dorsal surface of the ear pinna,[2] and the femoral, coccygeal, radial, and brachial arteries.[3] With practice, arterial catheterization and maintenance is not technically difficult and can provide information that helps guide lifesaving therapeutic interventions in the most critically ill veterinary patients.[3]

49.3 PATIENT PREPARATION

A patient's coagulation status should be considered carefully before arterial catheter placement. If a coagulopathy is not found or suspected, the site should be chosen based upon the patient's anatomy and consideration of underlying diseases, such as vomiting, diarrhea, pyoderma, or aural hematomas. For example, a radial arterial catheter may be inappropriate in a vomiting patient because of the risk of contamination. Similarly, femoral, coccygeal, or dorsopedal placement may be inappropriate in a patient with severe diarrhea. Patients with aural hematomas frequently shake their heads, and thus can easily dislodge an auricular arterial catheter, even when placed in a healthy ear. Because of the increased risks of auricular, coccygeal, and radial catheter dislodgement in ambulatory patients, dorsopedal catheters are preferred whenever possible.[1]

49.4 PERCUTANEOUS ARTERIAL CATHETER PLACEMENT

Once the proposed site of arterial catheterization has been chosen, the operator should become familiar with the animal's anatomy, palpating over the artery as it courses along the leg, tail, or ear while simultaneously feeling carefully for the arterial pulse. The designated site of catheterization should be clipped, then scrubbed aseptically with antimicrobial soap. The operator should perform careful hand washing and wear gloves to maintain aseptic technique during the procedure.

49.4.1 Percutaneous Dorsopedal Artery Catheterization

For dorsopedal artery placement, the patient should be positioned in lateral recumbency, and the leg with the proposed catheter site located down, adjacent to the table. The fur should be shaved on the anteromedial portion of the limb from the level of the tarsus distally along the length of the metatarsal bones. The artery usually is palpable just distal to the hock, between the second and third metatarsal bones.[1] Once the artery has been palpated and the site clipped and aseptically prepared, a 20- to 24-gauge over-the-needle catheter can be placed percutaneously or via percutaneous facilitation technique.

Percutaneous facilitation refers to the practice of making a small nick in the skin using the bevel of a 20-gauge needle. Use care to not penetrate the artery during this process because arterial spasm is common, and prevent cannulation until a palpable pulse returns. Whether the over-the-needle catheter is placed directly through the skin or through a nick incision formed by percutaneous facilitation, the needle and catheter should be inserted through the skin at a 15-degree to 30-degree angle over the palpable pulse.[1] The needle and catheter should be directed dorsally and laterally to the metatarsals over the site of a palpable pulse in small maneuvers, watching for a flash of blood in the catheter hub. Once a flash of blood is observed, the catheter should be pushed off of the stylet into the artery. Pulsatile arterial blood should be observed as soon as the stylet is withdrawn from the arterial catheter, if it is placed correctly.[1] Vasospasm may preclude further advancement in very small animals or cats, in which case a drop of papaverine hydrochloride can be flushed into the catheter to cause local vasodilation. If the catheter snags or does not feed easily, it can be pulled gently over the stylet and another attempt at catheterization performed (being careful not to pierce the catheter with the stylet).

In some cases when the original attempt catheterizes a vein, the catheter can be left in its original place and a second attempt performed proximally, if an arterial pulse is still palpable (Color Plate 49-1). Leaving the original catheter in place prevents hematoma formation that may preclude catheterization. Should all attempts at arterial catheterization fail, a pressure bandage should be placed for a minimum of 15 minutes to prevent hemorrhage and hematoma formation.[1]

Once the dorsopedal arterial catheter is in place, it should be flushed and secured as indicated in Box 49-1.

49.4.2 Femoral Artery Catheterization

Except for anatomic landmarks, percutaneous placement of a femoral arterial catheter is similar to that for the dorsopedal artery. The risk of hemorrhage is increased compared with other sites, however. The patient is placed in lateral recumbency, and the medial thigh clipped and aseptically scrubbed from the inguinal region distally to the stifle. The femoral arterial pulse is palpable on the medial thigh ventral to the inguinal region and proximal to the stifle. The over-the-needle catheter should be placed at a 20- to 30-degree angle through the skin and inserted in a proximal direction, watching carefully for a flash of blood in the catheter hub. Once a flash of blood is observed, the catheter should be advanced off of the stylette into the femoral artery. As the stylet is removed from the catheter, pulsatile arterial blood will be visible if the catheter has entered the artery. Once the catheter is placed, it should be flushed and secured as indicated in Box 49-1. Catheters in the femoral artery should also be secured with butterfly tape around the catheter hub, which is then secured to the patient's skin with sutures on either side of the hub.

49.4.2.1

Box 49-1 Procedure to Flush and Secure the Arterial Catheter

- A Luer-Lok T-port or male adapter flushed with preservative-free heparinized saline should be attached to the catheter hub to prevent further blood loss.
- The catheter should be flushed with preservative-free heparinized saline, then secured in place parallel to the artery using ½-inch and 1-inch white adhesive tape.
- The catheter hub and adjacent skin and fur should be carefully wiped dry of any blood and other liquids or debris before attempting to place tape around the catheter hub.
- The tape should be secured tightly around the catheter hub, to prevent dislodgement of the catheter. Additional lengths of 1-inch tape should be secured under the catheter hub and around the associated body part. Some clinicians use a combination of surgical glue, suture, and tape to secure the catheter, although this is not always necessary.
- The site of catheter insertion should be covered with antimicrobial ointment and bandage material, then labeled “Arterial Catheter—Not for IV Infusion” to prevent inadvertent injection of fluids or drugs into the arterial line.

49.4.3

Auricular Artery Catheterization

Catheterization of the auricular artery can be performed in dogs with large ears, such as hounds and hound mixes. The auricular artery lies on the dorsal surface of the ear pinna.[2] This type of catheter usually is placed while the patient is under heavy sedation or general anesthesia. The auricular arterial pulse can be palpated on the dorsal surface of the ear and the vessel traced toward the ear tip. The area over the artery should be clipped, then scrubbed aseptically. With the patient positioned in sternal or lateral recumbency, the ear is pulled gently such that the pinna is held perpendicular to the skull. The tip of the ear should be bent ventrally toward the operator such that the operator's fingers support the ear pinna from below. The artery is now bent at a perpendicular angle such that it can be traced from the point of a palpable pulse to the ear tip, and the over-the-needle catheter can be placed through the skin directly into the artery, with careful observation for a flash of blood in the hub of the catheter (Color Plate 49-2). Once a flash of blood is observed in the catheter hub, the catheter can be fed gently off of the stylet into the artery. Vasospasm may preclude further advancement in very small animals or cats, in which case a drop of papaverine hydrochloride can be flushed into the catheter to cause local vasodilation. Once the catheter is advanced into the artery, it should be flushed and secured as indicated in Box 49-1. In addition, the skin adjacent to the catheter hub should be dried carefully, and several drops of surgical glue placed adjacent to the catheter hub to help secure it to the skin. The ear can be supported from below with rolled up gauze 4 × 4-inch squares or rolls of gauze. Because the weight of the bandage is cumbersome, an awake and alert patient may attempt to shake its head, potentially causing catheter dislodgement. For this reason, the auricular arterial catheter is often limited to obtunded, comatose, or anesthetized patients.

49.4.4 Radial Artery Catheterization

The radial artery is technically more difficult to catheterize than those in other anatomic locations, but catheterization can be performed in large dogs. The patient should be placed in lateral recumbency, and the palmar aspect of the forelimb clipped just proximal to the large carpal pad, just distal to the accessory carpal pad, where the arterial pulse is palpable. The clipped area should be scrubbed aseptically. The operator should hold the patient's paw in one hand, palpating the arterial pulse with a thumb or forefinger. With the other hand, an over-the-needle catheter should be inserted through the skin at a 15-degree to 20-degree angle toward the palpable arterial pulse. The operator should watch carefully for a flash of blood in the catheter. As soon as a flash of blood is visible, the catheter should be pushed off the stylet into the artery. Once in place, the catheter should be flushed and secured as indicated in Box 49-1.

49.4.5 Coccygeal Artery Catheterization

The coccygeal arterial pulse is easily palpable on the ventromedial aspect of the tail just distal to the tail base. The fur over the palpable pulse should be clipped, then scrubbed aseptically. The patient can be positioned in dorsal or lateral recumbency, depending on operator preference. The arterial pulse should be palpated between coccygeal vertebrae and the over-the-needle catheter inserted through the skin at a 15-degree angle, pushing cranially toward the tail base until a flash of blood is seen in the hub (Color Plate 49-3). Once a flash of arterial blood is visualized, the catheter should be fed off the stylet, then flushed and secured as indicated in Box 49-1. Coccygeal catheters should be bandaged thoroughly to maintain cleanliness. Because coccygeal catheters become contaminated easily with the patient's feces during defecation and can become dislodged with patient movement, use of this site is limited largely to intraoperative procedures.

49.5 SURGICAL CUTDOWN FOR ARTERIAL CATHETER PLACEMENT

If percutaneous placement is unsuccessful, surgical cutdown can be performed to allow direct visualization and catheterization of the artery. Patient anatomy largely limits surgical cutdown procedures for arterial catheter placement to the dorsopedal and femoral arteries. Sterile technique should be used at all times. The area over the artery should be clipped and scrubbed aseptically, then draped with sterile field towels secured with towel clamps. A small bleb of 2% lidocaine should be injected into the skin and subcutaneous tissues, taking care to avoid intravenous or arterial administration of the local anesthetic.

The skin over the arterial pulse should be incised, taking care to avoid lacerating the artery and vein underneath the skin. The artery should be visible directly under the skin, surrounded by perivascular fascia. The dorsopedal artery usually is visible on top of the metatarsal bones.[3] Several drops of lidocaine should be placed directly over the artery to prevent arterial spasm as the perivascular fascia is bluntly dissected away from the vessel with a curved mosquito hemostat. Once the fascia has been removed from around the artery, a length of suture can be placed around the artery to help lightly elevate it parallel with the skin incision. It is very important to remove every bit of the perivascular fascia before attempting catheter placement.[1]

Once the artery has been elevated gently from the incision, the over-the-needle catheter can be inserted directly into the vessel, taking care to not penetrate through the other side. Excessive traction on the artery can cause arterial spasm, making catheterization difficult. A flash of blood will be observed in the hub of the catheter once the catheter has been introduced into the lumen of the artery. The catheter can then be fed off the stylet, flushed, and capped with a Luer-Lok T-port or male adapter. The suture that was used to elevate the artery can be used to secure the catheter to the vessel. The skin over the catheter should be closed with nonabsorbable suture, and the catheter taped in place, bandaged, and labeled as with any other arterial catheter (see Box 49-1).

49.6 MAINTENANCE OF THE ARTERIAL CATHETER

Depending on patient mobility, arterial catheters can be connected to a continuous flushing system with preservative-free heparinized saline, or flushed intermittently every 1 to 4 hours.[3] In extremely small patients, care must be taken to avoid excessive heparinization. As with other vascular catheters, arterial catheters should be examined on a daily basis for signs of erythema or infection. The area distal to the catheter should be palpated for any evidence of a coolness or pain, which indicate a compromise of blood flow. The bandage should be changed daily or more frequently as needed for soiling. Small volumes of preservative-free flush solution should be used to maintain catheter patency. However, other infusions (drugs or fluids or blood products) should never be administered into an arterial line.

Arterial catheters frequently cause vascular spasm and arterial occlusion in feline patients. Because cats have poor collateral circulation they are prone to developing ischemia subsequent to arterial catheter placement. It is therefore recommended that arterial catheters be kept in place for only 6 to 8 hours in feline patients.

49.7 THREE-SYRINGE SAMPLING TECHNIQUE

The three-syringe technique should be employed whenever a blood sample is obtained from an arterial catheter. To perform this technique, first flush the catheter with 0.5 ml of heparinized saline. Using the same syringe, withdraw 3 ml of blood from the catheter, and save it in a sterile manner, to be infused back into the patient through a peripheral venous catheter. Next, withdraw the desired volume of arterial blood into a heparinized or nonheparinized syringe. Finally, flush the arterial catheter with 2 to 3 ml of preservative-free heparinized saline, and clamp off or reconnect the T-port to the continuous flushing system. The arterial blood sample should be analyzed immediately or placed on ice for blood gas analysis.

49.8 SUGGESTED FURTHER READING*

MW Beal, D Hughes: Vascular access: theory and techniques in the small animal emergency patient. *Clin Tech Small Anim Pract*. **15**, 2002, 101, This is an excellent article that demonstrates step-by-step catheter placement and vascular cut-down procedures.

D Hughes, MW Beal: Emergency vascular access. *Vet Clin North Am Small Anim Pract*. **30**, 2000, 491, This is a good review of how to place intravenous catheters in an emergent patient.

LS Waddell: Direct blood pressure monitoring. *Clin Tech Small Anim Pract*. **15**, 2000, 111, This is a good article that describes placement of arterial catheters and direct monitoring of arterial and central venous pressures.

* See the CD-ROM for a complete list of references

50 Chapter 50 Pulmonary Artery Catheterization

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50.1 KEY POINTS

- Pulmonary artery catheters (PACs) are placed through the right side of the heart and the right ventricular outflow tract, into a pulmonary artery (PA).
- PACs may be used to measure cardiac output by thermodilution, to calculate systemic vascular resistance, and to sample mixed venous blood.
- Information from a PAC may be used to tailor fluid or pressor choices in the anesthesia or intensive care setting.
- A PAC may be placed by following pressure tracings or by using fluoroscopy.
- PA catheterization is not a benign procedure and may be associated with significant morbidity, requiring a thorough evaluation of the risk-to-benefit ratio.
- Many alternative techniques for measuring cardiac output that do not require a PAC are available for use in veterinary patients.

50.2 INTRODUCTION

Pulmonary artery (PA) catheterization is a technique that places a catheter through the right heart and right ventricular outflow tract into the PA. It is used to measure cardiac output by thermodilution, to calculate systemic vascular resistance, and to sample mixed venous blood. Often, placement is assisted by a latex balloon at the tip of the catheter that allows its course to follow the flow of blood (flow-directed catheter placement).

50.3 TYPES OF CATHETERS AND USES

There are many types of pulmonary artery catheters (PACs) designed for angiographic studies or for measuring the blood pressure in the pulmonary arteries. These catheters may be single-lumen or double-lumen catheters.[1] Some catheters designed to be introduced into the PA have sensors 4 cm distal to the tip of the catheter that allow temperature measurement (e.g., the Swan-Ganz type catheter). Other catheters may measure blood oxygenation (e.g., the oximetry thermodilution catheter) (Tables 50-1, 50-2, and 50-3). Diameters of thermodilution catheters range from 5 to 7.5 Fr. Angiographic catheters are available from 4 to 8 Fr. Most Swan-Ganz catheters are made of polyvinyl chloride (PVC) and are available in lengths of 75 or 110 cm, which are adequate for most small animal species, but which may not be of sufficient length for horses or other large animals. Other thermodilution catheters are made of polyurethane, which has the characteristic of softening at body temperature.

Table 50-1 Pulmonary Arterial Catheter Types, Sizes, and Manufacturers: Angiographic Catheters

Trade Name	Company	Diameter	Length
Berman angiographic catheter	Arrow Intl, Reading, PA	4 Fr	50 cm
		5 Fr	50, 60, 80 cm
		6 Fr	60, 90 cm
		7 Fr	90, 110 cm
		8 Fr	70, 110 cm
Double-lumen, pulmonary artery monitoring catheters	Edwards LifeSciences, Irvine, CA	5, 6, 7 Fr	110 cm
Pulmonary angiography catheters	Edwards LifeSciences, Irvine, CA	7 Fr	110 cm

Because of the wide diameter, complicated placement, and need to adjust the depth of catheter insertion, it is necessary to place PACs via a catheter introducer sheath. The introducer sheath should be at least one size larger than the catheter itself. For example, a 7 Fr catheter will fit through an 8 or 8.5 Fr introducer sheath, while a 6 or 6.5 Fr introducer sheath is adequate for the 5 Fr catheter. For sterility, a plastic sleeve attached to the sheath covers the catheter and keeps the catheter sterile while the PAC is moved into and out of the vessel.

Most commercial catheters designed for thermodilution measurement of cardiac output have multiple ports and lumens (Color Plate 50-1). The proximal port, or central venous pressure (CVP) port, is used to measure right atrial or central venous pressure. This port is also used for fluid boluses during cardiac output determination in humans, dogs, and cats. Because the proximal port is located 30 cm from the tip of the catheter where the thermistor is located, it is necessary to have a separate catheter advanced into the right atrium (RA) in large animals for the purpose of injecting fluid for thermodilution measurements (the proximal port will be located in the right ventricle [RV] in the horse).[2] Separate RA catheters have also been used in cats and small dogs, where the proximal port would be located outside of the RA.[3] When using separate injection catheters, it is important that the catheter volume be the same as the injection port on the Swan-Ganz catheter, because the K2 constant of the Stewart-Hamilton equation used by cardiac output computers is specific for the catheter type.[4] The distal port of the catheter is the central lumen and is used to measure both PA pressure and pulmonary capillary wedge pressure (PCWP) or PA occlusion pressure. Mixed venous blood is also sampled from this port. The balloon port allows for inflation of the balloon tip of the catheter with a small amount of air (usually ≤1.5 ml) for flow-directed catheter placement, and measurement of PCWP. The catheter will also have an electronic thermistor connection for temperature measurement.

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Table 50-2 Pulmonary Arterial Catheter Types, Sizes, and Manufacturers: Thermodilution Catheters

Trade Name	Company	Diameter	Length	Notes
Swan-Ganz	Edwards LifeSciences, Irvine, CA	5 Fr 6, 7, 7.5 Fr	75 cm 110 cm	Larger catheters have more lumina (up to 6) for infusion
		6, 7, 7.5 Fr	110 cm	
Opticath	Hospira Inc, Lake Forest IL	5.5 Fr	75 cm	—
		7.5, 8 Fr	110 cm	
Hands-off	Arrow Intl, Reading, PA	4 Fr	75 cm	Polyurethane, heparin coated
		5, 6 Fr	80 cm	
		6, 7, 7.5 Fr	110 cm	

Table 50-3 Pulmonary Arterial Catheter Types, Sizes, and Manufacturers: Other Catheters

Trade Name	Company	Additional Feature(s)	Diameter	Length
Opticath	Hospira Inc, Lake Forest, IL	SvO_2 probe plus Swan-Ganz	—	—
CCO, CCOmbo	Edwards LifeSciences	Continuous cardiac output, with or without SvO_2 monitoring	7.5, 8 Fr	110 cm
Oximetry thermodilution catheter	Edwards LifeSciences	Venous oxygen saturation (fiberoptic)	4 Fr	25, 40 cm
			5.5 Fr	75 cm
			7.5 Fr	110 cm
CCOmbo Volumetrics	Edwards LifeSciences	Volumetric (RVEDV), with SvO_2 monitoring and continuous cardiac output	7.5, 8 Fr	110 cm
Swan-Ganz pacing catheters, or Paceport catheters	Edwards LifeSciences	Pacing ability (or port for introduction of pacing electrodes)	7, 7.5, 8 Fr	110 cm

RVEDV, Right ventricular end diastolic volume; *SvO2*, venous oxygen saturation.

50.3.1 Cardiac Output

A PA catheter is necessary for evaluation of cardiac output using some thermodilution techniques (see Chapter 212, Cardiac Output Monitoring). Briefly, 1.5 ml/kg of saline (or 5% dextrose in water) of a known temperature is injected into the proximal port of the multilumen catheter.[4] In most animals, this proximal port (30 cm proximal to the tip of the catheter) will sit either in the RA or in the jugular vein, where it is appropriate to inject the indicator bolus. As mentioned previously, placement of a second injection catheter in the RA may be necessary to perform thermodilution in smaller or larger animals.[2,3] The thermistor probe on the distal end of the catheter will measure the change in blood temperature over time and will calculate cardiac output based on the area under the temperature curve. Newer Swan-Ganz catheters have thermistor probes near the junction of the proximal port and the catheter to more accurately measure the temperature of the injectate (it may warm significantly during injection). For larger animals such as horses, it is necessary to use chilled injectate, because subtle changes in blood temperature may not be sensed by the thermistor probe because of the relatively large cardiac output and blood volume in these animals. The indicator bolus must also be administered quickly, because a slow injection will minimize the change in temperature that is recognized by the thermistor and cause inaccurate readings (if injected too slowly, falsely low cardiac output measurement will be displayed). The use of a power injector pump is recommended for these measurements in large animals, and the bolus should be injected as quickly as possible in small animals.

50.3.2

Pulmonary Capillary Wedge Pressure

Measurement of PCWP via a PAC enables an estimation of left ventricular preload, because it can correlate with the left ventricular end-diastolic pressure. This correlation may not be reliable in patients with pulmonary hypertension, mitral regurgitation, or decreased ventricular compliance.[5,6] Airway and intrathoracic pressure can also affect this relationship. The methods for determination of the PCWP are discussed below. The PCWP may also be used to derive the pulmonary transcapillary pressure in dogs and cats.[4]

50.3.3

Right Ventricular End-Diastolic Volume

Right ventricular end-diastolic volume and index are used increasingly in human medicine to estimate volume status, especially in patients who are receiving positive-pressure ventilation with positive end-expiratory pressure, or other scenarios in which the PCWP does not accurately indicate left ventricular end-diastolic pressure. These values may be measured via catheters with special rapid-response thermistors that will sense small beat-to-beat changes in temperature induced by an upstream heat filament. These catheters need to be synchronized with the electrocardiogram, and patients need to have a regular R-R interval.[7] This same rapid-response thermistor and filament combination is used in catheters that will continuously measure cardiac output without the need for bolus injection (CCO PA catheter, CCOmbo Continuous Cardiac Output catheter, Baxter Healthcare Corporation, Edwards Critical Care Division, Irvine, CA).[7]

50.3.4

Selective Pulmonary Angiography

Selective pulmonary angiography via a PA catheter is sometimes indicated to elucidate complex congenital defects of the cardiopulmonary system in veterinary species.[1] Presurgical right heart catheterization for angiographic purposes is performed commonly in humans before cardiac surgery.[1] In animals, congenital defects such as stenosis of the pulmonic valve may be delineated via angiography and managed with balloon valvuloplasty by inflating a balloon catheter across the stenotic area.[8]

50.3.5 Additional Measurements

Balloon-tipped PACs that measure cardiac output and PCWP can also calculate systemic vascular resistance and pulmonary vascular resistance (see Chapter 212, Cardiac Output Monitoring).

50.4 INDICATIONS

The indications for placement of a PAC for the purposes of cardiac output measurement or mixed venous blood sampling have received much scrutiny in human medicine because of questions about the risk-to-benefit ratio. A 1997 consensus found a specific usefulness of the PAC in the management of hemodynamic instability during and after cardiac surgery and after myocardial infarction.[9] There was an uncertain benefit in the use of the PAC in defining shock states other than cardiogenic shock. Additionally, there was some evidence that the PA catheter was useful for treatment of trauma patients, as well as in certain pediatric populations.[9] A more recent study also questions the benefit of the PAC for management of heart failure, showing no benefit (but no detriment) in the group that had diuretic and afterload reduction therapy based on PAC measurements.[10] A recent metaanalysis of randomized controlled studies concluded that, although there was no increased morbidity in the PAC groups, a benefit was not realized from its use.[11,12] One reason that a clear benefit has not been shown for the PAC may be a result of inaccurate interpretation of the data obtained from the catheter.[13] Alternatively, the studies cited above evaluated a heterogeneous group of treatments, of which some may have been more effective than others.[14]

In veterinary medicine, catheters placed in the PA have been used for thermodilution measurement of cardiac output in many research studies.[15,16] The PAC seems useful for evaluation and treatment of cardiogenic shock. Information such as cardiac output and systemic vascular resistance can be used to guide inotropic and vasodilator therapy. Knowledge of systemic hemodynamics and cardiac output may also be helpful for guiding fluid resuscitation and pressor therapy in the small animal patient with hypovolemic and distributive shock. However, studies of the use of PACs in clinical veterinary patients are lacking.

Human data have focused on the optimization of oxygen delivery in shock and multiple organ dysfunction syndrome.[17] Although initial studies of this goal-directed therapy have been promising, the overall clinical benefit of this strategy compared with prior techniques has not been ascertained. Swan-Ganz catheters with oximetry probes are available to allow real-time measurement of venous oxygen saturation to allow optimization of oxygen delivery.

50.5 PLACEMENT

Judicious sedation using a benzodiazepine or an opioid may be indicated in some animals during placement of the introducer sheath and PAC. In the unanesthetized animal, a local block using lidocaine should be performed, because it is often necessary to make a skin incision to facilitate dilation of the vessel and smooth placement. Introducer sheath placement may be performed via a cutdown procedure to the external jugular vein, although percutaneous placement via a Seldinger technique is also appropriate and somewhat less complicated.[4] Before placing the catheter, a wide area of skin should be clipped and prepared aseptically. During placement, sterile drapes should be used to isolate the area, and sterile gowns, gloves, and a cap and mask should be worn.

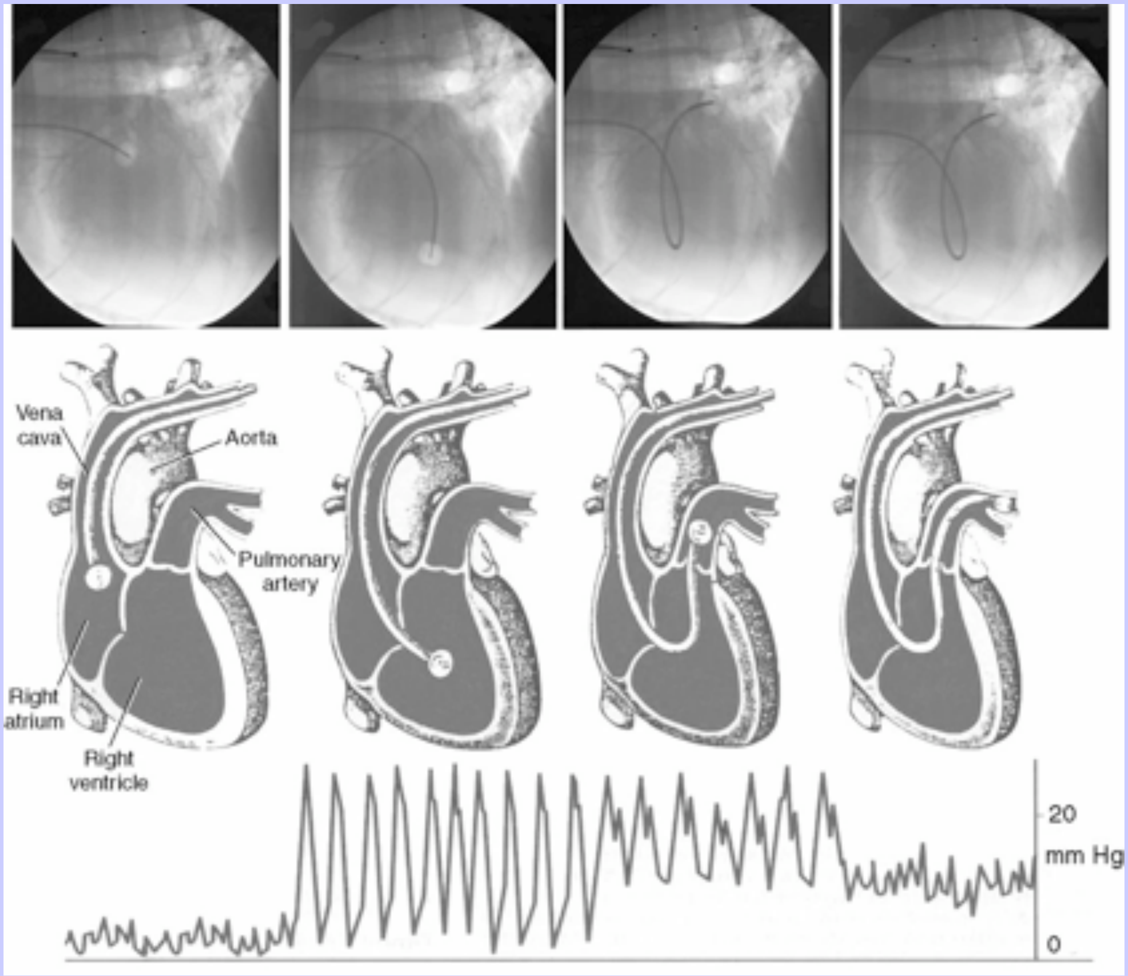
Regardless of technique, it is important to have an idea of the length of the catheter and distance from cardiac structures before placement. A lateral thoracic radiograph may be helpful for this purpose. Most Swan-Ganz thermodilution catheters are marked with thin black lines every 10 cm and thicker black lines every 50 cm (e.g., 70 cm is represented by one thick line and two thin lines, Figure 50-1). Placement is accomplished most easily through an introducer sheath placed in the external jugular vein.[5] The introducer catheter has a valve, which allows for ease of catheter placement and subsequent adjustments of catheter position, while preventing injection of air or loss of blood from the vessel. The addition of a sterile plastic sleeve allows for preservation of the sterility of the PAC during placement and adjustment. Once the introducer sheath is in place, the neck of the animal should be wrapped to protect the introducer sheath insertion site, as would be done with any jugular catheter.

Before feeding the PA catheter through the introducer sheath, the integrity of the balloon should be assessed. All ports of the catheter should be flushed with heparinized saline before introduction, and the catheter itself may be moistened with saline to allow smooth advancement through the introducer sheath.

50.5.1 Flow-Directed Placement

Classically, PACs are placed by attaching the distal port of the catheter to a calibrated pressure transducer and connected to a monitor. If continuous monitoring is to be performed, a system with a heparinized saline flush is indicated. By monitoring the pressure tracing as the catheter is advanced into the jugular vein (via the preplaced 211
introducer sheath), the position of the catheter tip may be deduced by recognition of the different waveforms 212
generated in each area of the heart and vessels (see Figure 50-1). After inserting the catheter into the RA (approximately 20 cm in a medium to large dog), the balloon may be inflated with air (the appropriate volume is usually listed on the port and is usually 1.5 cc) and then advanced further. It may not be necessary to inflate the balloon until the catheter tip is in the RV. The balloon should always be deflated before withdrawal of the catheter to prevent valvular damage or knotting of the catheter, and also after PCWP measurement to avoid unnecessary obstruction of blood flow.

Figure 50-1 The characteristic pressure waveforms recognized as the PAC is fed through (from left to right) the right atrium, the right ventricle, the pulmonary artery, and the wedge pressure tracing. Accompanied with a schematic and the fluorographic appearance at each step. In the fluorographic images, the dog is in right lateral recumbency with the dog facing left (NOTE: The third and fourth images are both in the pulmonary capillary). From Lalli SM: The complete Swan-Ganz, *RN* 41:64, 1978; and Headley JM: *Invasive hemodynamic monitoring: physiological principles and clinical applications,* Irvine, CA, 2002, Edwards Scientific.



In humans, the RA is entered at approximately 25 cm, the RV at approximately 30 cm, and the PA at approximately 40 cm; the PCWP can be identified at approximately 45 cm.[18] Thus, if 30 cm of catheter has been introduced but no atrial tracing is still seen, the catheter tip may have traveled into the azygous vein and should be withdrawn for another attempt. This may be avoided by keeping the tip directed ventrally, combined with slight rotation at the junction of the vena cava and the RA.[1] Once in the RA, the catheter may also become lodged in the coronary sinus or enter the caudal vena cava if it is directed too far caudally or dorsally.[1] If 10 cm has been introduced after attaining an RA tracing and the tracing has not changed, or reverts to a CVP tracing, inappropriate placement is suspected. Likewise, once in the RV, if the RV waveform persists 20 cm after initial appearance, the catheter may be coiling in the RV, and should be withdrawn slowly to the RA, after deflating the balloon, to avoid knotting of the catheter or damage to the tricuspid valve. Ventricular ectopic beats may be observed if the catheter contacts the walls of the RV. After the catheter has been floated into the PA, it should be pulled back 1 to 2 cm to straighten any redundant loops in the RV.

The pressure waveforms have characteristic tracings that allow the user to identify the position of the catheter tip. The RA tracing is similar to the CVP tracing from the jugular vein. Normal systolic RA pressure ranges from 4 to 6 mm Hg, with normal diastolic pressure from 0 to 4 mm Hg in anesthetized cats and dogs, giving a normal mean RA pressure of 2 to 5 mm Hg. Once the catheter is in the RV, a similar diastolic pressure is measured, but with a mean systolic pressure of 15 to 30 mm Hg. The PA tracing is notable because the diastolic pressure no longer decreases to zero because of the pulmonic valve, giving a mean diastolic pressure of 5 to 15 mm Hg (see Figure 50-1). Normal mean pulmonary artery pressure in dogs is 8 to 20 mm Hg.[1,15]

The characteristic waveform of the PCWP (similar to the RA tracing, but now representing the LA) is obtained by advancing the catheter slowly into the PA, with balloon inflated, until a point is reached when the diameter of the vessel is completely occluded by the balloon (see Figure 50-1). The waveform will change and the mean pressure will be lower than the mean PA pressure on entering the pulmonary capillary (mean PCWP is 5 to 12 mm Hg).[18] The catheter should not remain in a wedged position for longer than 10 to 15 seconds, or two respiratory cycles.[19] Once the PCWP is obtained, the balloon should be deflated, once again displaying the PA pressure waveform. For subsequent readings, because there is a tendency for the catheter to migrate distally as it warms to body temperature and softens, the balloon should be inflated slowly, with constant monitoring of the pressure tracing. PA rupture has been reported secondary to overzealous balloon inflation.[20] In humans, if a PCWP tracing is obtained before instillation of the full volume of air into the balloon (with less than 1.25 ml), it is recommended to deflate the balloon and to back the catheter out until PCWP is seen with full inflation of 1.5 ml of air.[18]

In the PA, the balloon should always be inflated slowly over 3 to 5 seconds, not only to avoid overinflation, but also because a rapid balloon inflation may be associated with spurious results.[18] If the pressure tracing shows a constantly increasing pressure, the tip of the catheter may be covered by the balloon, or may be pressed closely on the vessel wall or in a distal PA branch. This phenomenon, called over-wedging, may be remedied by deflating the balloon and situating the catheter tip more proximally before reinflating the balloon.

50.5.2 Fluoroscopy

Fluoroscopy provides a way to visually monitor catheter placement. PA catheters are radiopaque and so may be followed in their path from the jugular vein through the heart via radiography (see Figure 50-1). Fluoroscopy will help to quickly identify misplacement (e.g., into the azygous vein) and may enhance the speed of the procedure. The cons of fluoroscopy include the need for specialized equipment and generation of radiation during the procedure. All participants should wear protective lead aprons. Depending on the condition of the patient, it may not always be prudent to travel to a radiology suite to perform this procedure. Portable fluoroscopy units (C-arm) may simplify this procedure and move it closer to the bedside.

50.6 COMPLICATIONS

Complications of catheter placement reported in the human literature include wire or catheter embolus, cardiac tamponade, carotid artery puncture, hemothorax, and pneumothorax.[20] Many of these are related to the initial approach for vascular access (usually the internal jugular or subclavian veins), which is less of a problem in veterinary species with prominent external jugular veins suitable for placement of the introducer sheath. Insertion of the PA catheter into the mediastinum or the pleural space has also been reported in humans.[6] More serious complications associated with the PA catheter, although rare (estimated 0.0031%), include PA rupture from overzealous or erroneous balloon inflation or by direct catheter puncture. Risk factors for PA rupture in humans include advanced age, pulmonary hypertension, and improper inflation or positioning techniques.[6] Patients whose blood has been anticoagulated are also at risk. Little veterinary information is available about PA catheter complications; however, one postmortem study of horses after PA catheterization showed evidence of minor endocardial lesions.[21]

During catheter advancement through the heart, cardiac arrhythmias (premature atrial and ventricular contractions) may be seen. In humans, ventricular tachycardia and ventricular fibrillation have been reported, especially in patients with preexisting heart disease. Lidocaine was ineffective at suppressing these arrhythmias in one study, so the most effective way to decrease the incidence of ventricular ectopic beats is expedient passage of the catheter through the RV.[18] Right bundle branch block has also been reported during catheter advancement, which is of concern in patients with preexisting left bundle branch block, because complete heart block may result.[6] For this reason, it is recommended that the ability to perform transvenous or transthoracic pacing is available before performing this procedure in patients with left bundle branch block.[6] Some PA catheters are also equipped with a separate channel for the placement of pacing leads, and some have electrodes integrated into the catheter. Antiarrhythmic drugs should be available.

Once placed, maintenance of a PAC may be complicated by the formation of thrombi at the insertion site or at the tip of the catheter, or by embolic events from balloon rupture, inadvertent air administration, or thrombi, or distal catheter migration causing pulmonary infarction.[6,18] Infection is also a risk in patients with long-term indwelling PA catheters.[18] Anticoagulation is not routinely practiced after placement of a PA catheter, unless indicated for treatment of the underlying disease process. Anticoagulation in humans may be associated with increased severity of bleeding in the event of a PA rupture.[6] Heparin-coated PA catheters are available.[22]

50.7 ALTERNATIVES

Because of concerns related to the morbidity associated with PA catheters in critically ill patients, other techniques have been developed to measure cardiac output and systemic oxygenation. Direct measurements of ejection fraction and cardiac output may be obtained in anesthetized patients with transesophageal echocardiography, a technique that has been investigated in dogs,[23] but one which requires some skill in both obtaining and interpreting the images. Another technique for measuring cardiac output is similar to earlier indicator-dilution techniques that used indocyanine green dye as a marker of blood flow. With use of lithium chloride as a “dye,” concentrations measured by an ion-specific electrode may be analyzed and translated into cardiac output via a modified Stewart-Hamilton equation.[24,25] For cardiac output determinations using lithium dilution, the only necessary catheters are an arterial line for sampling and a central venous catheter for injection of the lithium chloride. Peripheral catheters may also be used for injection of the lithium chloride in dogs.[26] This technique has been investigated in dogs, cats, horses, and foals. Lithium ions do not reach toxic levels during routine use of this system.[27,28]

Some systems will derive continuous cardiac output measures via analysis of the arterial pressure waveform. The PulseCO system requires initial calibration with a cardiac output obtained via lithium dilution, and only periodic recalibration thereafter.[29] The PulseCO system has been evaluated in dogs and horses.[29,30] Newer systems (e.g., Flo-Trac, Edwards, Irvine, CA) do not require calibration to cardiac output.[31] A variation on the Fick principle, using partial carbon dioxide rebreathing, has also been developed to measure cardiac output. Termed *NiCO* (Respironics, Inc., Murrysville, PA), this technique uses a loop of tubing attached to the patient's endotracheal tube to measure the levels of expired carbon dioxide during a brief period of rebreathing.[32-34] An obvious detriment with use of this technique is the requirement of an intubated patient. This system has also been evaluated in dogs.[35]

Although a true mixed venous blood sample can not be obtained without a PAC, alternatives to measuring mixed venous oxygen saturation have been evaluated in human studies. The modification of goal-directed therapy using central venous oximetry has been proposed (see Chapter 10, Shock), and central venous catheters with fiberoptic oximetry probes are available for this purpose (PreSep Central Venous Oximetry Catheter, Baxter Healthcare Corporation, Edwards Critical Care Division, Irvine, CA).[17]

50.8 SUGGESTED FURTHER READING*

CMH Gomez, MGA Palazzo: Pulmonary artery catheterization in anaesthesia and intensive care. *Br J Anaesth*. **81**, 1998, 945, *An excellent human review article on placement, use, and pros and cons of the PAC.*

S Haskins, PJ Pascoe, JE Ilkiw, et al.: Reference cardiopulmonary values in normal dogs. *Comp Med*. **55**, 2005, 156, *A summary of many studies investigating the effects of various drugs on hemodynamic parameters in dogs.*

JM Headley: In *Invasive hemodynamic monitoring: Physiological principles and clinical applications*. 2002, Edwards Scientific, Irvine, CA, *An excellent monograph on use of and interpretation of data from PACs.*

M Mellema: Cardiac output, wedge pressure, and oxygen delivery. *Vet Clin North Am Small Anim Pract*. **31**, 2001, 1175, *An excellent chapter on hemodynamic monitoring, with special mention of cardiac output monitoring and PA catheterization.*

* See the CD-ROM for a complete list of references

51 Chapter 51 Temporary Transvenous Pacing

Teresa DeFrancesco, DVM, DACVIM (Cardiology), DACVECC

51.1 KEY POINTS

- Temporary transvenous pacing refers to a minimally invasive modality in which a pacing lead is inserted, either via the jugular or femoral vein, into the right ventricle. A current is generated from a temporary pulse generator that is external to the body.
- Indications for temporary transvenous cardiac pacing are emergency stabilization of a patient with symptomatic, medically refractory bradycardia, usually as a bridge to permanent pacing or when the bradycardia is transient or reversible, as with drug overdoses.
- Temporary transvenous cardiac pacing is preferred over the transcutaneous when pacing is required for longer than a few hours.
- The most common complication with temporary transvenous pacing is lead dislodgement and loss of capture. Other complications include thrombosis, bleeding, infection, ventricular arrhythmias, and cardiac perforation.

51.2 INTRODUCTION

Temporary transvenous cardiac pacing is a minimally invasive technique used primarily to correct profound medically refractory bradycardia in hemodynamically unstable patients.[1-3] Temporary cardiac pacing is also useful prophylactically to support heart rate and blood pressure in patients with sick sinus syndrome or high-grade atrioventricular block who are undergoing general anesthesia for permanent pacemaker implantation. The need for any type of temporary cardiac pacing for permanent pacemaker implantation is debatable in patients who are hemodynamically stable. However, in patients with erratic ventricular escape rhythms or with extremely low ventricular escape rates (<30 beats per minute [bpm]), temporary pacing does improve cardiac output and blood pressure during anesthesia until the permanent pacing system is in place.

Additionally, prophylactic use of temporary pacing during permanent pacemaker implantation ensures rapid rescue if problems such as asystole arise. Arguments against temporary transvenous pacing include increased surgical time, need for sedation for placement, and the lack of clear improved outcome. In a large retrospective review of artificial pacemaker practices and outcomes from seven veterinary institutions, the use of temporary transvenous pacing in patients undergoing permanent pacing varied from 4% to 100%, depending on the institution and personnel performing the procedure.[4] No complications from temporary cardiac pacing were reported in this case cohort. Complications, in general, from cardiac pacing were related primarily to the operator's experience level and frequency in placing artificial pacemakers.

Temporary transvenous cardiac pacing is the preferred modality in humans.[1,2] Advantages of the transvenous system, as compared with transcutaneous pacing, include more consistent capture, improved patient comfort, and relative ease of insertion by experienced personnel. In the veterinary arena, temporary transvenous pacing usually is available only at university or private specialty hospitals.

51.3 INDICATIONS FOR TEMPORARY TRANSVENOUS PACING

Indications for temporary transvenous pacing follow:

1. Support of heart rate and blood pressure is provided by temporary transvenous pacing while the patient is under general anesthesia during permanent pacemaker implantation.
2. A patient with medically refractory bradycardia that is in eventual need of a permanent pacemaker and requires hemodynamic support needs temporary pacing. Some of these patients are being stabilized until permanent pacemaker implantation is possible (e.g., personnel issues). Other patients may have systemic infection or endocarditis; thus permanent pacemaker implantation is being postponed until the patient is free of infection.
3. A patient with medically refractory and potentially reversible bradycardia, usually caused by a drug overdose, needs the hemodynamic support provided by a temporary transvenous pacemaker. Drugs that commonly cause medically refractory bradycardias include digoxin, diltiazem, verapamil, and β-blockers.

51.4 DESCRIPTION OF THE TEMPORARY TRANSVENOUS PACEMAKER

The equipment needed for temporary transvenous pacing includes a sheath introducer set, a temporary pacing lead wire, and a temporary pacemaker. Additionally, electrocardiography and, ideally, fluoroscopy are used to guide lead wire placement and identify ventricular capture.

The sheath introducer set includes a vascular access needle or catheter, placement wire, vessel dilator, and sheath introducer with a one-way hemostatic valve to allow passage of the lead wire. The diameter of the sheath introducer should be big enough to accommodate the pacing wire. The most common catheter size used by the author in dogs is 5 Fr.

The temporary pacing lead is usually a bipolar lead, although quadripolar electrophysiologic catheters are also available. The pacing lead can simply be a semirigid lead wire or can be associated with a balloon-tipped catheter to ease passage across the tricuspid valve. In humans, a new temporary pacing lead wire with active fixation has been described for long-term temporary pacing (days to weeks), such as in a patient with endocarditis.[5] These new active-fixation temporary wires dramatically decrease the rate of dislodgement in long-term temporary pacing.

The temporary pulse generator is a small hand-held battery-operated device in which heart rate, energy output, and sensitivity can be adjusted to the individual patient. This demand pacemaker allows sensing of the patient's intrinsic heart rhythm and subsequent suppression of the pacing impulse.

51.5 IMPLANTATION OF THE TRANSVENOUS TEMPORARY PACEMAKER

The dog is placed in lateral recumbency for central venous access. The need for sedation depends on the patient's demeanor and hemodynamic status. Either the jugular or femoral vein is cannulated aseptically with the sheath introducer, using the Seldinger technique. The author uses a small subcutaneous infusion of lidocaine for local anesthesia at the catheter insertion site. If using the jugular vein for temporary pacing, the left jugular is used to save the right jugular for the permanent system. Once the introducer is in place, it is flushed with heparinized saline and sutured in place.

The pacing lead wire is then inserted via the sheath introducer's hemostatic port, preferably through a plastic contamination guard. The wire is advanced into the right ventricular apex, ideally with fluoroscopic and electrocardiographic guidance, until ventricular capture is noted (Figure 51-1), associated with a smooth coursing of the lead wire into the apex of the right ventricle seen fluoroscopically. The pacing lead is connected to the external temporary pacemaker. The temporary pacemaker is usually set for a heart rate of about 80 to 100 beats/min. The energy output usually is set at 3 mA initially. At this voltage, the ventricle should be captured with each pacing impulse. One can determine the voltage threshold by gradually turning down the voltage until capture is lost. The pacemaker voltage is set at least twice the threshold voltage. The author typically sets the sensitivity at 3 V for temporary pacing, but this may need to be adjusted to ensure that no oversensing or, more importantly, undersensing of intrinsic beats occurs. Once the pacing wire and external temporary pacemaker settings are made and the lead wire position is deemed adequate, the insertion site is dressed with antimicrobial ointment and the neck is wrapped with a triple-layer bandage to ensure that the wire and external generator are secured and protected.

51.6 TROUBLESHOOTING

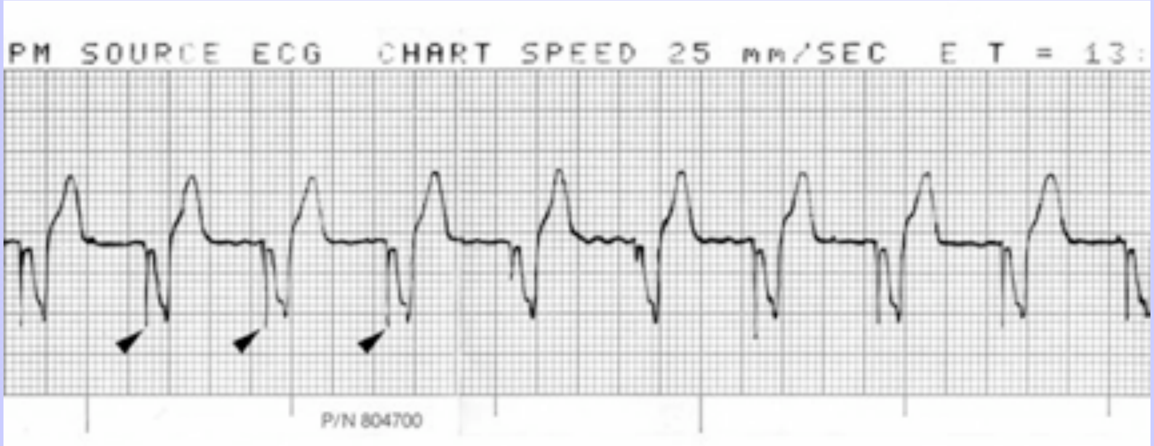
One potential problem with insertion is that the lead wire does not advance across the tricuspid valve into the right ventricular apex, and continues to loop in the right atrium or goes out the caudal vena cava. Balloon-tipped pacing catheters ease the passage across the tricuspid valve into the right ventricle. Additionally, before insertion of the wire, molding 3 to 4 cm of the tip of the wire to a gentle 20- to 30-degree angle may help slip it into the right ventricle.

The other common problem is inability to capture the ventricle. Pacing spikes are seen, but no QRS complex or capture is seen. This typically results from poor contact of the wire with the ventricular muscle. The position of the wire is checked using fluoroscopy. The ideal placement for the tip of the pacing wire is the apex of the right ventricle. If no pacing spikes are seen at all, then failure of the battery, pulse generator, or a loose connection is usually at fault. Ideally, a new battery is used for each case.

51.7 COMPLICATIONS

Lead dislodgement is the most common complication with temporary transvenous pacing, based on the human literature and the author's experience.[1,2,5,6] Lead dislodgement usually is well tolerated for brief periods but is potentially life threatening in a patient that is entirely pacemaker dependent. Interestingly, there are no reports of complications associated with temporary transvenous pacing in the veterinary literature. Several reports of complications associated with permanent transvenous pacing in dogs[4,7,8] describe similar complications that have been reported in the human literature for temporary transvenous pacing. These include hemorrhage, infection, ventricular arrhythmias, cardiac chamber perforation, and thrombosis. It is important to emphasize that although the serious complication rate is probably low for temporary transvenous pacing in dogs, there is the potential for significant and serious sequelae.

Figure 51-1 An electrocardiogram from a dog with a transvenous temporary pacemaker. Note the large pacing spikes *(arrows)* followed by QRS-T, confirming ventricular capture.



51.8 SUGGESTED FURTHER READING*

MD Kittleson, RD Kienle: Interventional anti-arrhythmic therapy. In *Kittleson MD, Kienle RD: Small animal cardiovascular medicine*. 1998, Mosby, St. Louis, *A nice overview and detailed description of transvenous cardiac pacing in the dog*.

MA Oyama, DD Sisson, LB Lehmkuhl: Practices and outcome of artificial cardiac pacing in 154 dogs. *J Vet Intern Med*. **15**, 2001, 229, *A large retrospective survey of pacing implantation techniques, complications, long-term outcome, and owner satisfaction in seven veterinary referral institutions*.

G Wess, WP Thomas, DM Berger, MD Kittleson: Application, complications and outcomes of transvenous pacemaker implantation in 105 dogs (1997-2002). *J Vet Intern Med*. **20**, 2006, 877, *A retrospective case review of pacemaker implantation, complications, and survival from one veterinary referral institution that commonly performs cardiac pacing*.

* See the CD-ROM for a complete list of references

52 Chapter 52 Transcutaneous Pacing

Teresa DeFrancesco, DVM, DACVIM (Cardiology), DACVECC

52.1 KEY POINTS

- Transcutaneous pacing (TCP) is a noninvasive modality of cardiac pacing in which patch electrodes are placed on the skin of the right and left hemithorax at the cardiac precordium. A current passed between these electrodes causes both electrical and mechanical capture of the heart.
- Indications for TCP are similar to those for temporary transvenous cardiac pacing—that is, emergency management of medically refractory and hemodynamically significant bradyarrhythmias, and support of heart rate and blood pressure of patients with sick sinus syndrome or high-grade atrioventricular block undergoing general anesthesia, typically for permanent pacemaker implantation.
- TCP is preferred over transvenous pacing in life-threatening situations because of the shorter time to implementation.
- The most common complications of TCP in dogs are discomfort and musculoskeletal stimulation associated with the pacing stimulus, which requires heavy sedation or general anesthesia. These limit its use for short-term temporary cardiac pacing.

52.2 INTRODUCTION

Transcutaneous pacing (TCP) is a noninvasive mode of temporary pacing used in patients with life-threatening, medically refractory bradyarrhythmias. TCP is also used to support cardiac output in patients with medically refractory bradyarrhythmias that are undergoing general anesthesia, typically but not exclusively for permanent pacemaker implantation. TCP is an attractive alternative to transvenous cardiac pacing for short-term pacing. Although transvenous cardiac pacing is well tolerated by most patients, it is an invasive procedure requiring considerable operator skill, and its use has been associated with serious complications in humans such as arrhythmias, infection, lead dislodgement, cardiac perforation, hemorrhage, and thromboembolism.[1,2]

TCP is preferred in emergency situations because of the shorter time to cardiac pacing.[3] TCP does not require vascular access. Vascular access, even with an experienced operator, can cause unacceptable delays in initiation of cardiac pacing. TCP was introduced in human patients during the 1950s and has been used routinely in acute care settings for approximately 20 years.[4,5] It was first described for use in client-owned dogs with medically refractory bradyarrhythmias in 2003.[6] Because of the cost of the equipment needed to implement TCP, the procedure usually is available only at selected university and private specialty veterinary hospitals.

52.3 INDICATIONS FOR TRANSCUTANEOUS PACING

Indications for TCP include emergency treatment of medically refractory and life-threatening bradyarrhythmias. Typical case scenarios include dogs with hemodynamically unstable complete AV block. In the author's experience, the dogs in this category are those with erratic ventricular escape rhythms in which many seconds can elapse with no ventricular contraction. TCP is also useful for an in-hospital cardiac arrest due to complete AV block or other medically refractory bradycardias in which a meaningful recovery can be expected.

A second indication for TCP is support of heart rate and blood pressure in dogs undergoing general anesthesia for permanent pacemaker implantation. Candidates are generally dogs with high-grade AV block or symptomatic sick sinus syndrome. TCP can also be used for permanent pacemaker replacement or readjustment of a dislodged lead wire. These dogs generally are hemodynamically stable at rest but have the potential for low cardiac output and even cardiac arrest while under general anesthesia. The TCP system typically is placed just before induction of general anesthesia and is in a ready state to implement for asystole, or simply for support of cardiac output if hypotension or extreme bradycardia occurs during the anesthetic period.

A third indication for TCP is support of heart rate and blood pressure in dogs with clinically silent sinus node dysfunction that have experienced an episode of profound and medically refractory bradycardia while undergoing general anesthesia. Typically these dogs were undergoing anesthesia for surgery unrelated to the heart, such as cataract extraction or cystotomy for urolithiasis removal, which was aborted because of the medically refractory and life-threatening bradycardia. If the owner or the dog's clinical status dictates that the surgery be reattempted, these dogs usually require temporary cardiac pacing to tolerate the anesthesia. The author generally does not recommend permanent pacemakers in dogs with asymptomatic sinus node dysfunction. The author believes TCP is a better option than transvenous cardiac pacing in these surgical cases because of its noninvasive nature and lower risk for infection.

52.4 DESCRIPTION OF A TRANSCUTANEOUS CARDIAC PACING SYSTEM

A TCP system is an optional feature on some defibrillator-electrocardiogram (ECG) systems. Currently, Medronic (Minneapolis, MN) and Zoll Medical (Chelmsford, MA) both offer optional external cardiac pacing. In addition to the pulse generator, the pacing system requires a good-quality ECG tracing and a pair of disposable transthoracic patch electrodes connected to the pulse generator via pacing leads.

Application of the external pacemaker is simple. Standard ECG leads usually are connected to the footpads of the 217
dog to obtain a good-quality recording. The adhesive pacing patch electrodes are then placed on the left and right 218
hemithorax directly over precordial impulse (Figure 52-1). The fur is shaved over both the left and right precordia, and a small amount of ECG paste is placed on the electrode patches just before adhesion. One may choose to further secure the patch electrodes with an elastic nonadhesive bandaging material to minimize migration and to improve contact. After the patch electrodes are placed, a good-quality ECG recording is obtained. Lead selection and ECG gain are optimized to attain accurate sensing of the patient's intrinsic cardiac rhythm by the demand pacing system (Figure 52-2). After accurate QRS sensing is confirmed by the appearance of the sensing marker on the ECG monitor, the desired pacing rate is chosen and the pacing current is increased gradually until ventricular capture is identified on the ECG (see Figure 52-2) and by palpation of a corresponding arterial pulse. 218
Determination of electrical and mechanical capture can at times be difficult because skeletal muscle is also 219
stimulated, causing motion ECG and palpation artifact, respectively. Ventricular capture is identified by a wide QRS-T complex after the pacing spike on the ECG monitor. The current output is then maintained just above the capture threshold, usually 10 to 20 mA greater than threshold, for the duration of cardiac pacing. In a clinical canine case series, the current required for pacing ranged from 50 to 110 mA.[6]

Figure 52-1 Schematic illustration of a dog under general anesthesia undergoing noninvasive, transthoracic external cardiac pacing. The dog is positioned in lateral recumbency, an electrocardiographic recording is obtained, and after proper sensing of the patient's cardiac rhythm, the pacing stimulus is delivered through the two large patch electrodes placed directly over the precordium on the right and left sides of the thorax. Illustration by Petra Guity. From DeFrancesco TC, Hansen BH, Atkins CE: Noninvasive transthoracic temporary cardiac pacing in dogs, *J Vet Intern Med* 17:663, 2003.

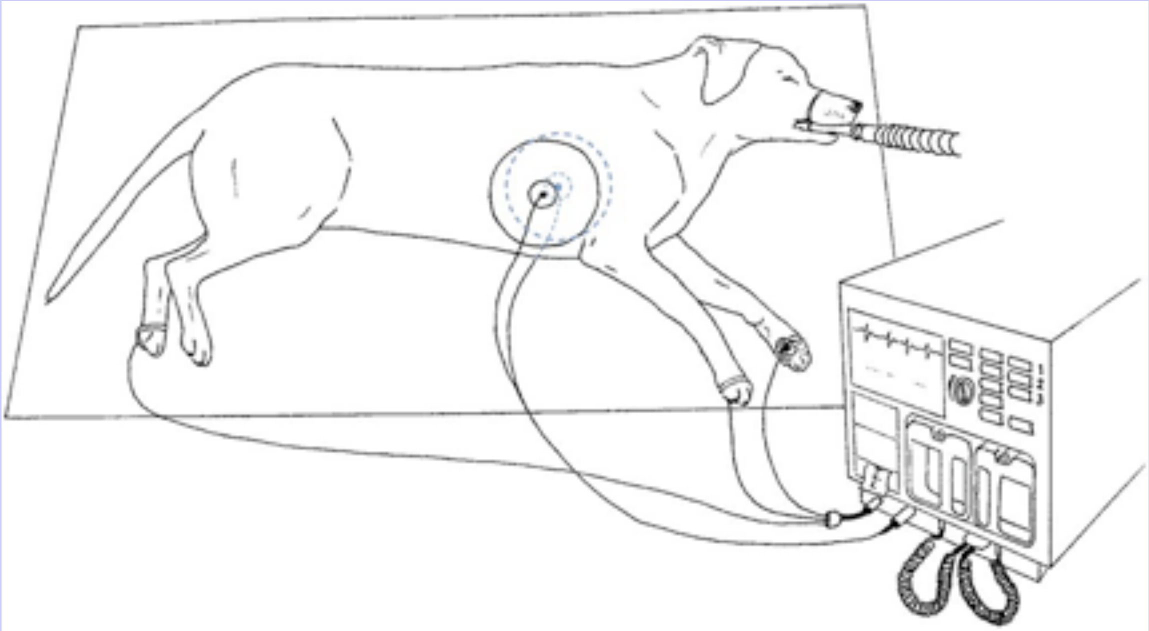
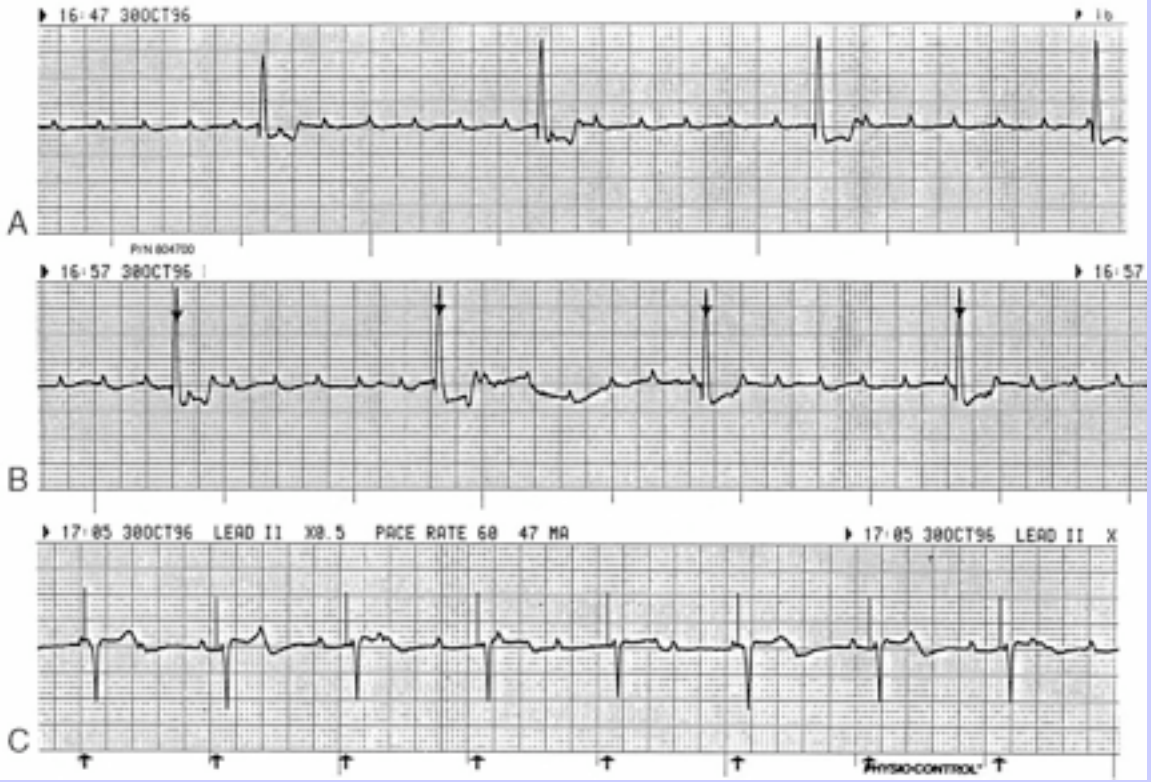


Figure 52-2 **A,** Electrocardiogram from a dog with complete atrioventricular block under general anesthesia for permanent pacemaker implantation. The ventricular rate is 30 beats/min while the atrial rate is 170 beats/min. **B,** Proper sensing of the patient's intrinsic QRS activity is shown with the sensing marker, an inverted triangular symbol on top of the QRS. Once accurate sensing is accomplished, the pacemaker is turned on. **C,** Electrical capture of the ventricle by the pacer is shown by a pacing spike followed by a wide QRS-T complex. Each pacing spike is also denoted by an *arrow* mark just below the paper grid. The ventricular rate is now 70 beats/min (paper speed for all ECG recordings is 25 mm/sec). From DeFrancesco TC, Hansen BH, Atkins CE: Noninvasive transthoracic temporary cardiac pacing in dogs, *J Vet Intern Med* 17:663, 2003.



52.5 COMPLICATIONS

Although most humans tolerate external cardiac pacing with no or minimal discomfort, conscious dogs, in the author's experience, do not tolerate TCP. General anesthesia and analgesia are strongly recommended for all dogs in which this technique is employed. In one human case series, the pacing stimulus was described as intolerable by only 10% of patients.[5] These patients described the pacing stimulus as a severe thump or as an intense burning or stinging pain that required termination of pacing. The pain and discomfort associated with noninvasive pacing are increased with higher pacing current outputs, smaller diameter patch electrodes, and presence of any skin abrasions at the electrode site.[5] It is unclear whether dogs truly feel pain with TCP or if the element of surprise, combined with the sudden and repetitive nature of the pacing stimuli and skeletal muscle stimulation, make the technique intolerable.

Despite the requirement for general anesthesia, TCP is a good alternative over temporary transvenous pacing in most veterinary clinical settings in which short-term temporary pacing is indicated, that is, permanent pacemaker implantation, replacement, or lead adjustment.

Skeletal muscle stimulation is another complication associated with TCP. This expected side effect is caused by unavoidable electrical stimulation of the skeletal muscles of the thorax and forelegs, which causes the patient to jerk mildly to moderately with each pacing impulse. These movements, although predictable, can increase the difficulty of surgery, especially in smaller dogs, in which the rhythmic motion of the forelegs can be more pronounced. This skeletal muscle jerking can be eliminated with neuromuscular blockade, which then necessitates mechanical ventilation during anesthesia.

52.6 TROUBLESHOOTING

Despite the ease and speed of noninvasive transthoracic pacing, especially in arrest situations, the primary disadvantage in human patients is inconsistent pacing success rates.[7] In the author's experience, initial failure to pace in dogs with TCP usually results from suboptimal electrode placement. The patch electrodes should be placed directly over the cardiac impulse beat, but not too close to the sternum, so that the current actually courses across the heart and not along the skin. The author has also noted that skin and, subsequently, the patch electrodes tend to move with changes in body position, which can cause loss of capture. The position of the patch electrodes should be checked every time the dog is moved. The user also should be aware that the patch electrodes are available in adult and pediatric sizes, and that the appropriate electrode size should be used for the dog. Other causes of inconsistent pacing include obesity, barrel-shaped chest conformation, and pleural space or pericardial disease. In dogs with physical reasons for inconsistent pacing, increased current, generous use of conducting gel, and chest wrap with a nonadherent bandaging material usually help to achieve capture. In a canine case series, successful pacing was achieved in all dogs, although repositioning of the patch electrodes was needed in several patients.[6]

52.7 SUGGESTED FURTHER READING*

TC DeFrancesco, BH Hansen, CE Atkins: Noninvasive transthoracic temporary cardiac pacing in dogs. *J Vet Intern Med*. **17**, 2003, 663, *Retrospective case review of 42 client-owned dogs, the first description of transcutaneous cardiac pacing in veterinary medicine. Also describes the TCP system and how optimal patch electrode placement was determined in the dog.*

V Kaushik, AR Leon, JS Forrester, Jr.: Bradyarrhythmias, temporary and permanent pacing. *Crit Care Med.* **28**(10 Suppl), 2000, N121, *A nice human review article describing common bradyarrhythmias and indications for pacing. Review and comparison of the various modalities for temporary and permanent cardiac pacing.*

JD White, CG Brown: Immediate transthoracic pacing for cardiac asystole in an emergency department setting. *Am J Emerg Med.* **3**, 1985, 125, *Evaluates the effectiveness of transthoracic pacing for human cardiopulmonary arrest and suggests that transcutaneous pacing may be preferable for resuscitation to avoid significant delays.*

* See the CD-ROM for a complete list of references

53 Chapter 53 Cardioversion and Defibrillation

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53.1 KEY POINTS

- Defibrillation and cardioversion involve the application of an electrical shock to terminate a cardiac arrhythmia.
- Electrical defibrillation is a key component of advanced life support and is the only effective treatment for ventricular fibrillation or pulseless ventricular tachycardia in patients with cardiopulmonary arrest. Chemical defibrillation is not a viable alternative.
- Synchronized cardioversion is used for treatment of unstable or drug-refractory supraventricular or ventricular tachyarrhythmias and delivers the electrical impulse at a specific portion of the cardiac cycle to avoid the vulnerable period during the T wave.
- Defibrillator use poses some risk to staff and should be done by trained personnel following a standard protocol.

53.2 INTRODUCTION

Electrical defibrillation and cardioversion are advanced techniques that involve the application of an electrical shock to terminate a cardiac arrhythmia. Both of these techniques use current generated from a defibrillator to cause simultaneous global depolarization of the myocardium, thereby interrupting rhythms that depend on organized or disorganized reentrant mechanisms for their maintenance.[1] Although defibrillation and cardioversion are very similar, they differ somewhat in their application.

Specifically, *defibrillation* refers to an unsynchronized impulse delivered in an effort to abolish ventricular fibrillation or pulseless ventricular tachycardia and is a key component of advanced life support and cardiopulmonary resuscitation (CPR) (see Chapter 4, Cardiopulmonary Resuscitation). In comparison, *synchronized cardioversion* refers to an impulse that is delivered during a specific portion of the cardiac cycle to terminate a symptomatic supraventricular or ventricular arrhythmia.

It should be noted that defibrillation and cardioversion are used to treat symptomatic and potentially life-threatening arrhythmias. In cardiopulmonary arrest associated with a rhythm of ventricular fibrillation or pulseless ventricular tachycardia, the use of a defibrillator is unquestioned and is likely the only method that may restore spontaneous circulation. For other arrhythmias, including sustained, symptomatic supraventricular or ventricular tachycardia, the role of electrical therapy is not clearly defined for veterinary patients in an emergency or critical care setting. Certainly cardiac arrhythmias are common in critically ill dogs and cats and are associated with primary cardiac disease as well as with a variety of noncardiac conditions. However, most of these arrhythmias, including isolated single ventricular premature complexes or accelerated idioventricular rhythms, do not require specific therapy. When the arrhythmia requires management, drug therapy is the appropriate therapeutic choice for nearly all patients. Only in rare situations is the emergency use of synchronized cardioversion indicated. In all cases, patients that are successfully defibrillated or cardioverted should be monitored intensively and treated aggressively to prevent deterioration of their postshock rhythm.

53.3 EQUIPMENT

Many newer defibrillators have the capability to perform both synchronized cardioversion and defibrillation. Defibrillators are available from many manufacturers in both portable and stand-alone configurations. Ideally, the defibrillator is placed on a crash cart in a centrally located arrest station along with supplies for vascular access, airway management, and resuscitation drugs. Although both defibrillation and cardioversion may be performed with standard paddles, several accessories make the procedures easier to perform in veterinary patients. First, an attachment called a *posterior paddle* (Color Plate 53-1), which is a flat paddle that can be placed under the patient, makes it possible to cardiovert or defibrillate a patient in lateral recumbency. This minimizes the awkwardness and increased danger to staff that arises from defibrillating a patient in dorsal recumbency. Second, many defibrillators can be used with adhesive patches instead of paddles. These patches come in both pediatric and adult sizes for use on both small and large patients and provide similar benefits to a posterior paddle.

53.3.1 Monophasic Versus Biphasic Waveforms

Two types of defibrillators are available: monophasic and biphasic. These differ by the shape of the waveform that is generated by the defibrillator. Monophasic defibrillators generate a single positive current, and biphasic defibrillators generate a positive followed by a negative current (Figure 53-1). The bidirectional energy flow produced by biphasic defibrillators allows lower energy settings to be employed, and there is evidence suggesting that this technology allows for more efficient defibrillation with less myocardial damage.[2] Although biphasic defibrillators are becoming more common in human medicine and recommendations for energy settings have been incorporated into human CPR guidelines,[3] monophasic defibrillators are much more common in veterinary hospitals. Accordingly, guidelines for energy settings in small animal patients are based on defibrillators with monophasic waveforms.[4]

53.4 SAFETY

Electrical defibrillators can be among the most effective, as well as the most dangerous, pieces of equipment in a veterinary hospital. Inadvertent delivery of current to staff can result in painful electrical shocks, burns, and potentially serious cardiac arrhythmias. The risk of injury to staff increases when the animal is in dorsal recumbency, because it is more likely that the patient's limbs will touch nearby personnel. It is also important to recognize that metal surfaces may conduct current, and it is recommended that nonconducting rubber or foam pads be placed on metal tables near the crash cart. Additionally, poor contact between the paddles and the chest may result in arcing of current across the surface of the patient. This can result in fire, especially when alcohol has been placed on the fur. As a result, only contact gel should be used to apply electrocardiogram (ECG) electrodes when defibrillation or cardioversion may be necessary. Because of these potential hazards, it is vital that staff members are educated in the use of the defibrillator and that protocols for cardioversion and defibrillation are followed carefully.

53.5 DEFIBRILLATION

53.5.1 Indications

The indications for defibrillation are clearly defined: ventricular fibrillation or pulseless ventricular tachycardia in a patient suffering cardiopulmonary arrest. Once either of these rhythms is recognized, ongoing CPR should be halted and defibrillation should take place immediately. Other arrest rhythms, including asystole, sinus bradycardia, or slow pulseless electrical activity, are not indications for defibrillation. Although ventricular fibrillation is the initial arrest rhythm in only 20% of small animal patients suffering cardiopulmonary arrest,[5] it often develops during the course of the resuscitation, and the defibrillator should be immediately available if this occurs.

Figure 53-1 Monophasic *(left)* versus biphasic *(right)* defibrillator waveforms.

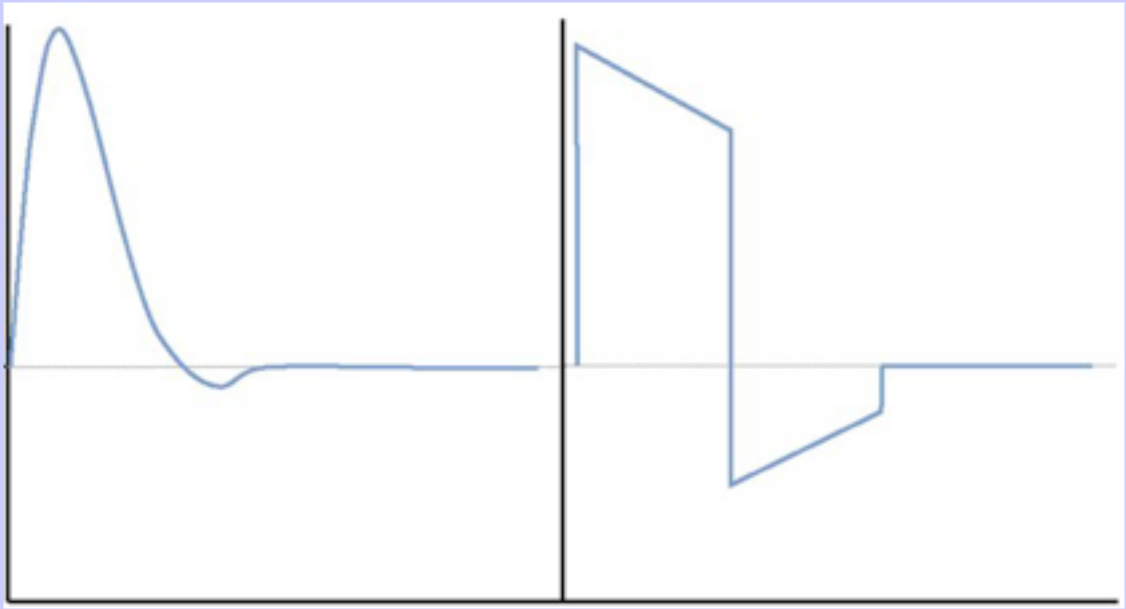

Table 53-1 Guidelines for Initial Defibrillator Settings With Monophasic Waveform Defibrillators

	Weight (lb) Weight (kg)	52.5	10 5	2010	30 15	4020	50 25	60 30	70 35	80 40	90 45	100 50
Dosage												
External defibrillation	2 to 10 J/kg	20	30	50	100	200	200	200	300	300	300	300
Internal defibrillation	0.2 to 1 J/kg	2	3	5	10	20	20	20	30	30	30	30

53.5.2 Technique for Use

Defibrillation may be performed in conjunction with both closed-chest and open-chest CPR techniques. External defibrillation is performed most commonly and, as mentioned above, may be done with standard defibrillator paddles, a standard paddle and a flat posterior paddle, or adhesive defibrillator patches. The author's preferred technique is a standard paddle and a flat posterior paddle, with the patient in lateral recumbency. This eliminates the awkward and dangerous use of dorsal recumbency necessary with two standard paddles and is quicker and more consistent to perform than the use of adhesive patches, which requires clipping of hair and is prone to poor skin contact if traction is applied to the leads. With the patient in right lateral recumbency, the posterior paddle is placed underneath the right side of the chest and a standard paddle is used on the upper side. A generous amount of contact gel is applied to each paddle before use, and care is taken to place the paddles over the heart (as opposed to the dorsal portion of the chest wall).

Before delivering countershocks, it is important that the operator follow a sequence designed to ensure the safety of all personnel participating in the resuscitation effort. First, the ECG rhythm of ventricular fibrillation or pulseless ventricular tachycardia is verified. Second, proper placement of the paddles is confirmed. Third, the operator announces the intention to defibrillate the patient, halt ongoing CPR, and calls “clear.” Fourth, following the call of “clear,” the operator visually confirms that no personnel are in contact with the patient or table. Finally, firm pressure is applied with the paddle and the countershock is delivered. The ECG is then monitored for the efficacy of the countershock, and the patient is immediately reassessed for the return of spontaneous circulation.

An energy setting of 3 to 5 joules/kg (range 2 to 10) is selected for the initial external defibrillation attempt (Table 53-1), with an increase in energy of approximately 50% for each subsequent attempt. It had previously been recommended that a series of three shocks be administered before recommencing CPR (for 1 to 2 minutes) in cases of unsuccessful defibrillation, with pauses between shocks only long enough to monitor the ECG and to recharge the defibrillator.[4,6] More recent human recommendations call for 1 to 2 minutes of CPR between each unsuccessful shock, because this may increase the likelihood of success.[3] It is reasonable to adapt these guidelines to veterinary patients, and the one-shock protocol may be considered an alternative to the established three-shock protocol.

Defibrillation may be performed during open-chest CPR. In this situation, internal paddles are employed to apply current directly to the epicardium. Accordingly, the energy used is significantly less than that used for external defibrillation. An initial energy of 0.2 to 1 joule/kg is selected, and this may also be increased by 50% with subsequent shocks. As with external defibrillation, a one-shock or three-shock protocol may be used, with 1 to 2 minutes of cardiac compression between defibrillation attempts with the one-shock method. Because myocardial burns may occur with internal defibrillation, it is recommended that saline-soaked gauze sponges be placed between the paddles and the epicardium before defibrillation. Although the energy used for internal defibrillation is significantly less than for external defibrillation, it is still important to follow standard protocol to ensure safety of all personnel before discharge of the defibrillator. It should also be mentioned that if internal paddles are not available, the patient may still be defibrillated externally in standard fashion during open-chest resuscitation.

53.6 CARDIOVERSION

53.6.1 Indications

As opposed to defibrillation, the indications for synchronized cardioversion are less well defined in small animal patients. In human medicine, synchronized cardioversion is the emergency treatment of choice for unstable patients with supraventricular or ventricular tachyarrhythmias.[3] Most dogs and cats with sustained tachyarrhythmias can be treated successfully with antiarrhythmic drugs (see Chapter 190, Antiarrhythmic Agents). Although synchronized cardioversion for dogs with “lone” atrial fibrillation has been described,[7] this is not considered an emergency procedure and, if it is considered, should be performed by a veterinary cardiologist.

In patients with atrial fibrillation and a rapid ventricular response rate, management with rate-lowering drugs (calcium channel blockers, β-blockers, digoxin) is more appropriate in an emergency setting.

Synchronized cardioversion is indicated, however, in patients with sustained supraventricular or ventricular tachyarrhythmias that are unresponsive to drug therapy and result in adverse clinical signs. This is especially true if the arrhythmia is compromising perfusion and causing signs of shock or hypotension, because the rhythm may deteriorate rapidly to ventricular fibrillation. In all conscious patients, sedation and analgesia or anesthesia must be provided, because cardioversion is a painful and distressing procedure in an awake patient.

53.6.2 Technique for Use

Synchronized cardioversion, like defibrillation, may be performed with standard defibrillator paddles, with a standard paddle and a flat posterior paddle, or with adhesive patches. Because synchronized cardioversion often is performed in more controlled circumstances than is defibrillation, the author prefers to clip the fur on either side of the thorax and to use adhesive defibrillator patches. Following the administration of sedatives and analgesics or the rapid induction of anesthesia, the patient is placed in lateral recumbency. As with defibrillation, a protocol is followed to ensure the safety of the staff before administering the countershock. The key components are to announce the intention to perform cardioversion, to call “clear,” and to visually verify that all personnel are clear of the patient and table before discharge.

The defibrillator should be placed in synchronization mode, and it should be verified that the QRS complexes are recognized. Most defibrillators display a mark on each recognized complex as it is displayed on the ECG monitor. The energy to be used for synchronized cardioversion is not well defined for veterinary patients. However, because cardioversion requires less energy than defibrillation, it is recommended to begin with 50% of the energy recommended for defibrillation.[4,7] This is similar to guidelines for human medicine and has proven effective in veterinary patients.[3,6,7] Once the countershock has been delivered, the ECG should be monitored for resolution of the arrhythmia and, if persistent, cardioversion may be repeated at the same or sequentially increasing energy levels.

Synchronized cardioversion prevents delivering the countershock during the vulnerable period associated with the mid to late portion of the T wave. The vulnerable period represents the relative refractory period, during which the ventricular myocardium is in various stages of repolarization. During this time, stimulation of reentrant circuits can lead to ventricular fibrillation.[8] Despite the synchronization feature of the defibrillator, it is possible for the rhythm to deteriorate during cardioversion. Because of this, it is important to be prepared to perform immediate defibrillation (at standard energy levels) should ventricular fibrillation develop or to perform CPR should asystole occur. In patients that are cardioverted successfully, appropriate antiarrhythmic therapy should be instituted, and the patient should be monitored intensively for recurrence of the arrhythmia.

53.7 POSTDEFIBRILLATION AND CARDIOVERSION MONITORING

In addition to continuous ECG monitoring and appropriate antiarrhythmic therapy, patients should be monitored for systemic derangements that may result from temporary tissue ischemia. The neurologic status of post-defibrillation or cardioversion patients should be assessed and monitored, because cerebral anoxia or emboli may occur. Respiratory rate and effort, in addition to oxygenation status, should be observed because CPR and central nervous system disease may affect respiratory function and drive, respectively. Arterial blood pressure should be maintained within a normal range to maximize oxygen delivery to the tissues and prevent organ dysfunction. Skin burns should be identified and treated with appropriate wound care.

53.8 SUGGESTED FURTHER READING*

JM Bright, JM Martin, K Mama: A retrospective evaluation of transthoracic biphasic electrical cardioversion for atrial fibrillation in dogs. *J Vet Cardiol*. **7**, 2005, 85, *The only published retrospective analysis of synchronized cardioversion in dogs*.

SG Cole, CM Otto, D Hughes: Cardiopulmonary cerebral resuscitation in small animals: a clinical practice review. Part II. *J Vet Emerg Crit Care*. **13**, 2003, 13, *A review of and guidelines for veterinary cardiopulmonary cerebral resuscitation in small animal patients*.

JL Jones, OH Tovar: Electrophysiology of ventricular fibrillation and defibrillation. *Crit Care Med*. **28**, 2000, N219, *A brief review of electrophysiologic mechanisms responsible for ventricular fibrillation and electrical defibrillation*.

* See the CD-ROM for a complete list of references

97 Chapter 97 Coma Scales

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97.1 KEY POINTS

- Coma can result from many causes affecting the intracranial nervous system.
- Severe head trauma is a common cause of coma in veterinary medicine, and victims may have a poor prognosis.
- The prognosis for a patient with head trauma depends on the severity of the neurologic injury at the time of hospital admission.
- Neurologic injury can be categorized numerically based on the abnormalities detected on examination.
- The numeric scoring system developed for animals with head injury is the modified Glasgow Coma Scale.
- The scoring system is based on specific abnormalities of mentation, motor function, and neuroophthalmologic examination.

97.2 INTRODUCTION

Although coma can be caused by an array of direct and indirect neurologic disorders affecting the intracranial structures in small animals. The development of coma scales has focused on dogs and cats with head trauma. These tools can be used objectively to decide when to initiate aggressive treatment, to monitor the success of therapy and, in some cases, provide a prognosis. Such scoring systems are in their infancy in veterinary medicine and are meant to be only a guide to management. They can be used to monitor patients with any cause of coma based on this premise. This chapter is focused on coma scales as they specifically relate to head trauma.

Appropriate therapy for patients with head trauma remains controversial in veterinary medicine (see Chapter 152, Traumatic Brain Injury). Treatment must be immediate if the animal is to recover to a level that is both functional and acceptable to the owner. It is important therefore to be aware of the optimal way to assess these patients; many dogs and cats can recover from severe brain injuries if the clinician is able to identify treatable systemic and neurologic abnormalities in a timely manner.

97.2.1 Intracranial Pressure After Head Trauma

Increases in intracranial pressure (ICP) are often responsible for the clinical decline seen in many animals after head trauma.[1] Following traumatic brain injury, the volume of the brain tissue compartment increases, usually a result of edema or hemorrhage. As this tissue compartment increases, the cerebrospinal fluid (CSF) and blood compartments must decrease to prevent an increase in ICP. Compensation for increased brain tissue volume initially involves shifting of cerebrospinal fluid out of the skull, decreased production of CSF and, eventually, decreased cerebral blood flow.[2] These compensatory mechanisms prevent increases in ICP for an undetermined period. In general, the compensation is more effective when the increases in ICP are slow. Once the capacity for compensation is exhausted, a further small increase in intracranial volume will result in dramatic elevations of

ICP, with the immediate onset of clinical signs.[2] Unfortunately, the clinical signs of significantly increased ICP often become evident too late for any therapy to be effective. A clear understanding of what clinical signs necessitate immediate intervention, those that indicate a grave prognosis, and those that need to be closely monitored will help with the successful treatment of patients following head trauma.

97.3 NEUROLOGIC ASSESSMENT

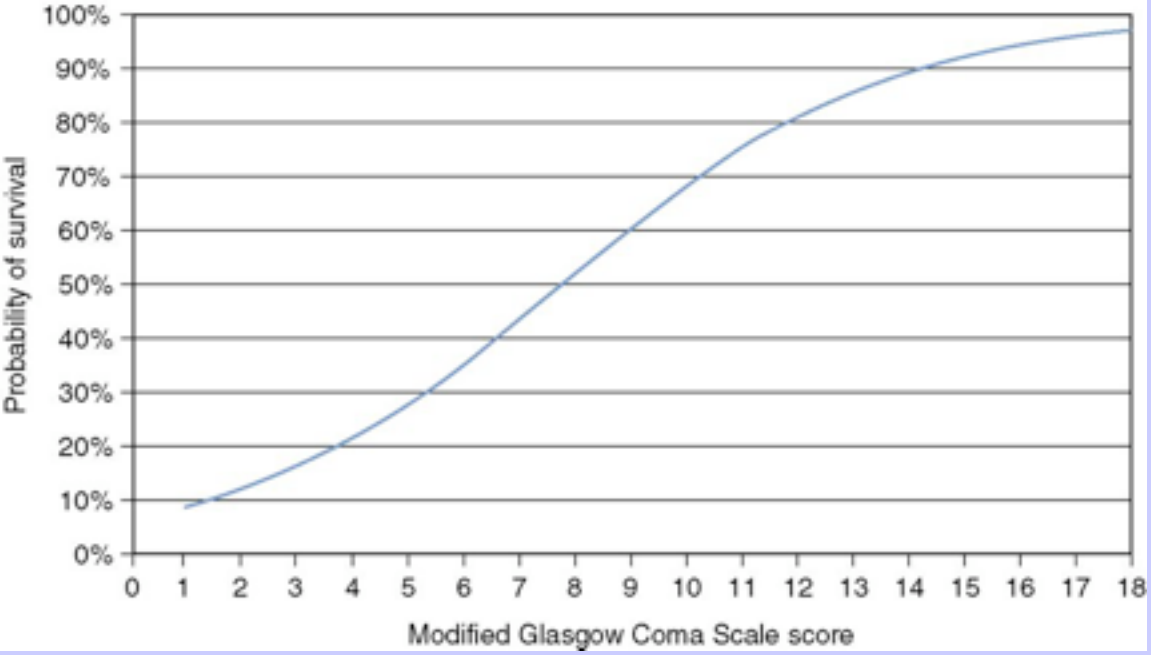
Initial neurologic assessment should include an evaluation of the patient's state of consciousness, breathing pattern, size and responsiveness of pupils, ocular position and movements, and skeletal motor responses. This should be repeated at least every 30 to 60 minutes in patients with severe head injuries to assess for deterioration or to monitor the efficacy of therapy. This would require an objective mechanism to “score” the patient's condition so that treatment decisions could be made logically.

97.4 MODIFIED GLASGOW COMA SCORING SYSTEM

In humans, traumatic brain injury is graded as mild, moderate, or severe on the basis of the level of consciousness or the Glasgow Coma Scale.[3] Mild traumatic brain injury in humans is usually due to a concussion, and full neurologic recovery routinely occurs. A patient with moderate traumatic brain injury is lethargic or stuporous, and a patient with severe injury is comatose. Patients with severe traumatic brain injury have a high risk of hypotension, hypoxemia, and brain swelling.[3] If these sequelae are not prevented or managed properly, they can exacerbate the existing brain damage and increase the risk of death.[3] The clinical point at which to initiate therapy for a veterinary patient with head trauma, the extent of appropriate therapy, and the length of time that such treatment is necessary are poorly documented. The effectiveness of specific treatment and the prognosis for any given animal will always be difficult to assess because of the multifactorial nature of the injury.

A modification of the Glasgow Coma Scale used in humans has been proposed for use in veterinary medicine.[4]
This scoring system enables grading of the initial neurologic status and serial monitoring of the patient. Such a 410
system can facilitate the assessment of prognosis, which is crucial information for both the veterinarian and owner.[4] 411
An almost linear correlation between this scoring system and survival of dogs with head trauma has now been evaluated (Figure 97-1).[5] It should be noted that long-term survival and functional outcome have not been evaluated using these scales in dogs or cats.

Figure 97-1 Probability of survival for patients with head trauma based on their individual modified Glasgow Coma Scale score at admission. Reprinted with permission from Platt SR, Radaelli ST, McDonnell JJ: The prognostic value of the modified Glasgow Coma Scale in head trauma in dogs, *J Vet Intern Med* 15:581, 2001.



Each of the three categories of the examination (i.e., level of consciousness, motor activity, brain stem reflexes) is assigned a score from 1 to 6 (Table 97-1). The level of consciousness provides information about the functional capabilities of the cerebral cortex and the ascending reticular activating system in the brain stem.[6]

97.4.1 Levels of Consciousness

The level of consciousness is the most reliable empiric measure of impaired cerebral function after head injury. Impairment of consciousness is stratified in terms of the responses to external stimuli, and serial records of these responses are an important clinical guide to treatment.

The consciousness level of is also a valuable index of injury severity. In the early evaluation, the depth of impairment can be used as a measure of cerebral impairment. Levels of consciousness range from normal, depressed, or delirious, to stuporous or comatose. Depression is a reduced state of mental function. A delirious animal manifests a reduced state of consciousness with profound disorientation. Stupor is partial or nearly complete unconsciousness, manifested by response only to vigorous or noxious stimulation. Coma is a state of unconsciousness from which the patient cannot be aroused.

Decreasing levels of consciousness indicate abnormal function of the cerebral cortex or interference with transmission of sensory stimuli by the brain stem ascending reticular activating system. Patients that arrive in a state of coma generally have bilateral or global cerebral abnormalities or severe brain stem injury and have a guarded prognosis.[7]

97.4.2 Limb Movements, Posture, and Reflexes

Spontaneous and evoked limb movements are studied as part of the coma scale examination.[5] It is important for the clinician to determine whether spinal cord injury or severe orthopedic abnormalities are present before extensive manipulation of the patient. Motor activity may be affected by the animal's level of consciousness; the best motor response detected is the most important. Animals that are not comatose, but have an altered state of consciousness, usually maintain some voluntary motor activity.

Muscle tone is assessed by putting the limbs through a full range of passive movement, keeping in mind the possibility of a long bone fracture. The tendon reflexes are elicited; these reflexes have very little value in the diagnosis of acute cerebral injuries, but localized absence of tendon jerks may disclose a nerve injury. Exaggerated reflexes can be seen in all four limbs in most patients with cerebral injury (or cervical spinal cord trauma), but severely affected comatose animals lose muscle tone and reflex activity.

Opisthotonus with hyperextension of all four limbs is suggestive of decerebrate rigidity (Color Plate 97-1), whereas variable flexion and extension of the hind limbs is seen in rigidity with cerebellar injury (Color Plate 97-2).[7,8] Decerebrate rigidity, occasionally seen in animals recumbent as a result of craniocerebral trauma, can provide further information about the severity of the brain injury.[4]

97.4.3 Neuroophthalmologic Examination

97.4.3.1 Pupils

This is the basis of the brain stem reflexes category. Pupil size, shape, and reactivity are recorded routinely during the initial examination and should be checked at frequent intervals thereafter. If the pupillary light reflex is impaired on one side, the contralateral light reflex is tested to see whether the impaired pupil reacts consensually. In the unconscious patient, changes in the pupillary light reactions often give diagnostic information regarding the cerebral condition and prognosis.[6] The light reflex may also be the only available test of optic nerve function (Table 97-2). It is necessary to use a strong light source and to shield the opposite eye when testing for a consensual response.

Pupillary abnormalities may be bilateral or unilateral; they may be present from the time of the injury or may appear later. Mild size discrepancy between the two pupils (<3 mm) has not been significantly associated with 411 patient outcome in humans.[9] Pupils that are widely dilated at the time of initial examination may indicate an 412 irreparable primary midbrain lesion or advanced herniation. However, there are other causes that should be ruled out. These include the following: the early postictal period, inadequate cerebral perfusion,[10] local trauma to the iris or its innervation on both sides prior administration of opioid (cats only) or anticholinergic therapy, or the use of a mydriatic agent to view the fundus. Previous ocular disease may be associated with bilateral or unilateral pupillary abnormalities. In humans, bilateral optic nerve injury may result in bilateral fixed or sluggish pupils, sometimes with autonomic balance fluctuations causing spontaneous fluctuations (hippus) in diameter.[10]

Table 97-1 Small Animal Modified Glasgow Coma Scale

Assessment Parameter	Score
Motor Activity	
Normal gait, normal spinal reflexes	6
Hemiparesis, tetraparesis, or decerebrate activity	5
Recumbent, intermittent extensor rigidity	4
Recumbent, constant extensor rigidity	3
Recumbent, constant extensor rigidity with opisthotonus	2
Recumbent, hypotonia of muscles, depressed or absent spinal reflexes	1
Brain Stem Reflexes	
Normal pupillary light reflexes and oculocephalic reflexes	6
Slow pupillary light reflexes and normal to reduced oculocephalic reflexes	5
Bilateral, unresponsive miosis with normal toreduced oculocephalic reflexes	4
Pinpoint pupils with reduced to absent oculocephalic reflexes	3
Unilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes	2
Bilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes	1
Level of Consciousness	
Occasional periods of alertness and responsiveness to environment	6
Depression or delirium, capable of responding but response may be inappropriate	5
Semicomatose, responsive to visual stimuli	4
Semicomatose, responsive to auditory stimuli	3
Semicomatose, responsive only to repeated noxious stimuli	2
Comatose, unresponsive to repeated noxious stimuli	1

Reprinted with permission from Platt SR, Radaelli ST, McDonnell JJ: The prognostic value of the modified Glasgow Coma Scale in head trauma in dogs, *J Vet Intern Med* 15:581, 2001.

A score is given to each of three categories of the neurologic examination: motor activity, brain stem reflexes, and level of consciousness. Within each category, a score of 1 to 6 exists, representing the most severe to the mildest of clinical pictures. A total score can then be helpful (1) in estimating the severity of the initial condition, which determines the most appropriate level of therapy, (2) assessing the prognosis for survival within the first 72 hours, and (3) assessing the effect of therapy.

Pupils that respond appropriately to light, even if miotic, indicate adequate function of the rostral brain stem, optic chiasm, optic nerves, and retinas. In the absence of concurrent ocular trauma, miosis may indicate a diencephalic lesion, particularly in the hypothalamus, because this area represents the origin of the sympathetic pathway.[4,7,8] In humans who have sustained head trauma, bilateral miosis has also been associated infrequently with pontine lesions.[10]

Table 97-2 Anatomic Interpretation of Pupillary Abnormalities

Injury	Ipsilateral Pupil	Associated Findings
Oculomotor nerve	Dilated and fixed to direct light No consensual constriction from contralateral light but normal consensual constriction in contralateral pupil	Ptosis and ventrolateral strabismus
Optic nerve	Fixed to direct light Absent consensual constriction in contralateral pupil Normal consensual constriction from contralateral light	Spontaneous fluctuations in pupil size
Oculomotor and optic nerve	Dilated and fixed to direct light No consensual constriction from contralateral light and no consensual constriction in contralateral pupil	Ptosis and ventrolateral strabismus
Iris or ciliary body	Dilated and fixed to direct light No consensual constriction from contralateral light but normal consensual constriction in contralateral pupil	Often signs of orbital injury No strabismus
Cervical sympathetic pathway	Constricted and fixed or sluggish to direct light and contralateral light but normal consensual constriction in contralateral pupil	Ptosis

Pupils that are initially miotic and then become mydriatic are indicative of a progressive brain stem lesion, whereas bilateral mydriasis with no response to light is usually indicative of irreversible midbrain damage, herniation of the cerebellum through the foramen magnum, or both.[7] Unilateral mydriasis may indicate unilateral cerebellar herniation or brain stem hemorrhage.[6,7] However, a unilateral mydriasis and loss of direct light reflex in one eye commonly implies a cranial nerve III paralysis, and is commonly accompanied by ptosis and ventrolateral strabismus (see Table 97-2). In humans this can be a sign associated with extradural bleeding and warrants immediate advanced imaging.[11]

97.4.3.2 Eye Movements

In the unconscious patient, spontaneous ocular movements should be assessed.[5] If there are none, the
oculocephalic reflexes (i.e., physiologic nystagmus) are tested by rotating the head in vertical and horizontal 412
planes. This can be done only when a cervical spinal injury has been excluded. Oculocephalic reflexes may be 413
impaired in animals with brain stem lesions as a result of either involvement of cranial nerve nuclei that innervate the extraocular muscles or the interconnecting ascending medial longitudinal fasciculus within the pons and midbrain.[11]

In addition to their localizing value, the eye movements have been considered indices of head injury severity. The ability of the patient to fix its eyes on a target and follow it is a favorable finding, and absence of eye movements is an ominous finding. Absence of eye movements on irrigating the external auditory canal with ice-cold water (oculovestibular reflex) is indicative of profound brain stem failure and is an accepted criteria of brain death in humans.[10] However, such a test should not be performed if there is any suspicion of a craniotaural fistula or a skull base fracture. Between the presence and absence of inducible eye movements, there are many ill-defined disturbances with unknown diagnostic and prognostic implications.[10]

97.5 COMA SCALES AND LONG-TERM FUNCTIONAL OUTCOME

There have been no long-term functional outcome studies in dogs or cats following head trauma, so the use of coma scales for long-term prognosis is not documented. There is an obvious need for an accurate assessment of outcome, because patients surviving head trauma may be left with multiple neurologic deficits that markedly affect the quality of life (or at least the owner's perception of the animals quality of life). Exceptional owner commitment may enable some very disabled patients to return home, but minor neurologic deficits may be viewed by some owners as unacceptable.

A standardized outcome scale used in human medicine is the Glasgow Outcome Scale.[12] This scale is based on the overall social capability of the patient, which takes into account specific mental and neurologic deficits. It was devised for victims of brain damage in general, because it was required for studies both of head injury and of atraumatic coma. Four categories of survival are recognized and are listed as good recovery, moderate disability (independent but disabled), severe disability (conscious but dependent), and vegetative state.[12] There is variation within each category, but much of this may not be applicable to veterinary patients because it is based on the ability of the patient to communicate and be self-sufficient. There is a need, however, for the modified Glasgow Coma Scale to be correlated with an outcome scale in veterinary medicine, because this would truly assist with defining a prognosis in small animal patients. Until this time, coma scales can be used only as a guide of the immediate success of therapy and, more importantly, when to initiate this treatment.

97.6 SUGGESTED FURTHER READING*

RS Bagley: Intracranial pressure in dogs and cats. *Comp Cont Educ Pract Vet*. **18**, 1996, 605, *Excellent overview of intracranial pressure in normal and disease states.*

AL Hopkins: Head trauma. *Vet Clin North Am Small Anim Pract*. **26**, 1996, 875, *Comprehensive review of the pathophysiology and management of head trauma in cats and dogs.*

SR Platt, ST Radaelli, JJ McDonnell: The prognostic value of the modified Glasgow Coma Scale in head trauma in dogs. *J Vet Intern Med*. **15**, 2001, 581, *Retrospective study that demonstrates an almost linear relationship between the modified Glasgow Coma Scale Score and patient survival in dogs.*

* See the CD-ROM for a complete list of references

98 Chapter 98 Seizures and Status Epilepticus

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Richard A. LeCouteur, BVSc, PhD, DACVIM (Neurology)

98.1 KEY POINTS

- Epilepsy refers to recurrent seizures of any type resulting from an intracranial cause and may be subdivided into true epilepsy (inherited, acquired, and idiopathic) and symptomatic epilepsy.
- Seizures are classified as partial or generalized; generalized seizures are the most common.
- Status epilepticus (SE) is a life-threatening neurologic emergency, and a common initial complaint at the emergency hospital.
- SE may cause serious systemic problems such as hypoxia, hyperthermia, systemic lactic acidosis, shock, and acute renal failure.
- Disorders that induce seizures and SE are either extracranial or intracranial.
- A complete history, physical examination, neurologic examination, and minimum database should be done in all animals with a seizure disorder.
- Further investigation of intracranial diseases using electroencephalography, magnetic resonance imaging, or computed tomography imaging, cerebrospinal fluid analysis, serology, and biopsy may be indicated.
- Seizure management is based on control of seizures by selection and appropriate administration of an anticonvulsant drug. When an underlying disease is present, it should be treated concurrently. Seizures associated with SE should be stopped as quickly as possible.

98.2 INTRODUCTION

The epidemiology of seizures in cats and dogs is unknown, despite reports of the rate,[1] prevalence,[2] and incidence.[3] Population-based animal studies are difficult to execute, thus most studies are based on data from groups of veterinary hospitals or referral-based veterinary teaching hospitals.[2] The epidemiology of seizures in groups of purebred dogs or colonies of research dogs[1] with epilepsy has been reported. For example, one population-based study reported the lifetime prevalence of epilepsy in the Danish Labrador as 3.1% (95% confidence interval 1.6% to 4.6%).[4] Although these studies are interesting, the information cannot be extrapolated beyond the research colony, hospital, or specific purebred dog geographic setting.

Despite the lack of prevalence or incidence data, it is accepted that seizure disorders are common in dogs and cats and that seizures occur more frequently in dogs than in cats. Estimates of lifetime seizure frequencies are 0.5% to 5.7% in dogs and 0.5% to 1.0% in cats.[5]

Status epilepticus (SE) is a life-threatening neurologic emergency and a common presenting complaint at an emergency hospital. Although the population prevalence of SE is not known, in one report the prevalence of SE and cluster seizures in dogs was 0.44% of all hospital admissions.[6]

Although many different types of seizures occur in dogs and cats, a classification system that is accepted universally by veterinary neurologists has not been established.[7-9] To effectively diagnose and treat dogs and cats with seizure disorders, including SE, it is important to understand the terminology, pathophysiology, and causes of seizures.

98.2.1 Definitions

A *seizure* is the clinical manifestation of a paroxysmal cerebral disorder, caused by a synchronous and excessive electrical neuronal discharge, originating from the cerebral cortex.[5]

Cluster seizures are two or more seizures within a 24-hour period.[6]

Epilepsy is recurrent seizures of any type resulting from an intracranial cause.[5]

1 *True epilepsy* originates from a nonprogressive intracranial disorder.[5]

  A Inherited epilepsy is caused by a genetically determined intracranial disorder.[5]

  B Acquired epilepsy is caused by a previously active intracranial disorder that is no longer active.[5]

  C Idiopathic epilepsy is a seizure disorder in which the cause and mechanism for the seizures is unknown.[5]

2 *Symptomatic epilepsy* is caused by progressive intracranial disease.

Status epilepticus is a neurologic emergency requiring immediate therapy. A universally accepted definition for SE in humans or animals does not exist.[6,10] The authors recommend the definition, “continuous seizures, or two or more discrete seizures between which there is incomplete recovery of consciousness, lasting at least 5 minutes.”[11]

98.3 CLASSIFICATION

Seizures in dogs and cats may be classified as partial or generalized, based on clinical observations rather than EEG characteristics. Partial seizures originate from a focus in one cerebral hemisphere and usually manifest localized clinical signs. Partial seizures usually have an acquired cause and may be subdivided into simple partial seizures or complex partial seizures. In simple partial seizures there is no alteration in consciousness, and the clinical signs during the seizure are limited to isolated muscle groups (e.g., tonus or clonus of a limb). Additional clinical signs (e.g., autonomic signs) may be present during a simple partial seizure. Complex partial seizures are accompanied by an alteration in consciousness. There may be involuntary or compulsive actions such as chewing, licking, and defensive or aggressive behavior. Complex partial seizures have been referred to as psychomotor seizures. Both types of partial seizures may spread throughout the brain, causing generalized seizures.[5] 414 415

Generalized seizures are the most commonly recognized seizures in dogs and cats. The most common type is the tonic-clonic seizure. Other types of generalized seizures such as tonic, clonic, or myoclonic seizures are recognized. In tonic-clonic seizures, animals lose consciousness. In the tonic phase, increased muscle tone results in limb and head extension, causing the animal to fall to the side. In the clonic phase, alternating extension and flexion of the limbs, and exaggerated chewing movements, occur. The animal usually urinates, defecates, and salivates.[5]

98.4 PATHOPHYSIOLOGY

The normal brain is capable of seizures in response to a variety of intracranial and extracranial stimuli. When the brain's homeostasis is overcome, cerebrocortical excitability is altered and the seizure threshold is decreased. Normal animals with a low seizure threshold may be induced to have a seizure by many factors, including fatigue, fever, estrus, photic stimulation.

Experimentally, repeated stimulation of the rat cerebral cortex by a subconvulsive electrical stimulus caused generalized seizures over time. This phenomenon is referred to as *kindling*. [12] Following establishment of a focal seizure focus, abnormal electrical activity may be recorded over the contralateral cerebral cortex. This secondary seizure focus is termed a *mirror focus*. [13] Either the primary or secondary focus, or both, may cause seizures. The mirror focus may cause seizures even if the primary seizure focus is removed.[14] Although kindling and mirror foci are observed as experimental phenomena, they may be clinically relevant in the therapy of animals with seizure disorders.

In SE, there is failure of the normal brain homeostasis mechanisms that work to stop seizures. Proposed mechanisms for the development of SE include persistent neuronal excitation, inadequate neuronal inhibition, or both.[11] Extrasynaptic factors may be important in spreading and maintaining the seizure. An excess of excitatory neurotransmitters such as glutamate, aspartate, or acetylcholine, or antagonists of γ-aminobutyric acid (GABA) (an inhibitory neurotransmitter) may cause SE.

SE lasting 30 to 45 minutes results in brain injury in experimental animals.[15] However, brain injury probably occurs in clinical patients after a much shorter time. SE may cause neuronal necrosis, particularly in brain regions with high metabolic rates. In one report, neuronal necrosis was most severe in rats that were hypoxemic or exhibited tonic-clonic seizures.[16]

In early SE, an increase in cerebral blood flow may be protective for the brain. In late SE, cerebral blood flow decreases simultaneously as blood pressure decreases, and cerebral metabolic rate (e.g., glucose and oxygen utilization) increases. This leads to adenosine triphosphate depletion and lactate accumulation, which contribute to neuronal necrosis. SE may be associated with systemic problems including hypoxemia, hyperthermia, aspiration pneumonia, systemic lactic acidosis, hyperkalemia, hypoglycemia, shock, cardiac arrhythmias, neurogenic pulmonary edema, and acute renal failure.

98.5 ETIOLOGY

Disorders that induce seizures and SE arise either outside the nervous system (extracranial) or within the nervous system (intracranial). Extracranial causes may be divided into those that originate outside the body (e.g., toxins) and those that originate within the body but outside the nervous system (e.g., liver disease). Intracranial causes of seizures are divided into progressive and nonprogressive diseases.[5]

Extracranial causes may result in generalized seizures, because they affect the brain globally. Causes of progressive intracranial disease include inflammation (e.g., granulomatous meningoencephalitis), neoplasia, nutritional alterations (e.g., thiamine deficiency), infection, anomalous entities (e.g., hydrocephalus), and trauma. Most animals with progressive intracranial disease are clinically abnormal between seizures and usually have progression of clinical signs. However, seizures may be the only clinical sign for a prolonged time, before others become apparent.

Nonprogressive causes of seizures include inherited, acquired, and idiopathic epilepsy. Dogs with inherited epilepsy usually are 6 months to 5 years of age. Many breeds are known or suspected to have inherited epilepsy.[17] In idiopathic epilepsy, seizures are caused by a functional problem of the brain and therefore are generalized and symmetrical.

Very few veterinary studies have evaluated the clinical features of SE; therefore it is not possible to make generalizations concerning underlying causes or concerning short-term and long-term outcomes. One study[18] evaluated a cohort of 50 dogs with SE. Of those, 28% had idiopathic epilepsy, 32% had symptomatic epilepsy, and 12% had seizures secondary to a systemic insult or to physiologic stress. Forty-four percent of the dogs had not had SE previously. Many dogs were euthanized, and thus a mortality rate was not reported.[18] In another study[19] of SE in dogs with idiopathic epilepsy, 59% of the dogs had one or more episodes of SE. Survival time was shorter in dogs with both idiopathic epilepsy and SE than in those with idiopathic epilepsy alone.[19] In another study of SE or cluster seizures in dogs, a poor outcome was reported in dogs with granulomatous meningoencephalitis, poor seizure control after 6 hours of hospitalization, or SE manifest by partial seizures. Fifty-nine percent of the dogs in this study died or were euthanized.[6]

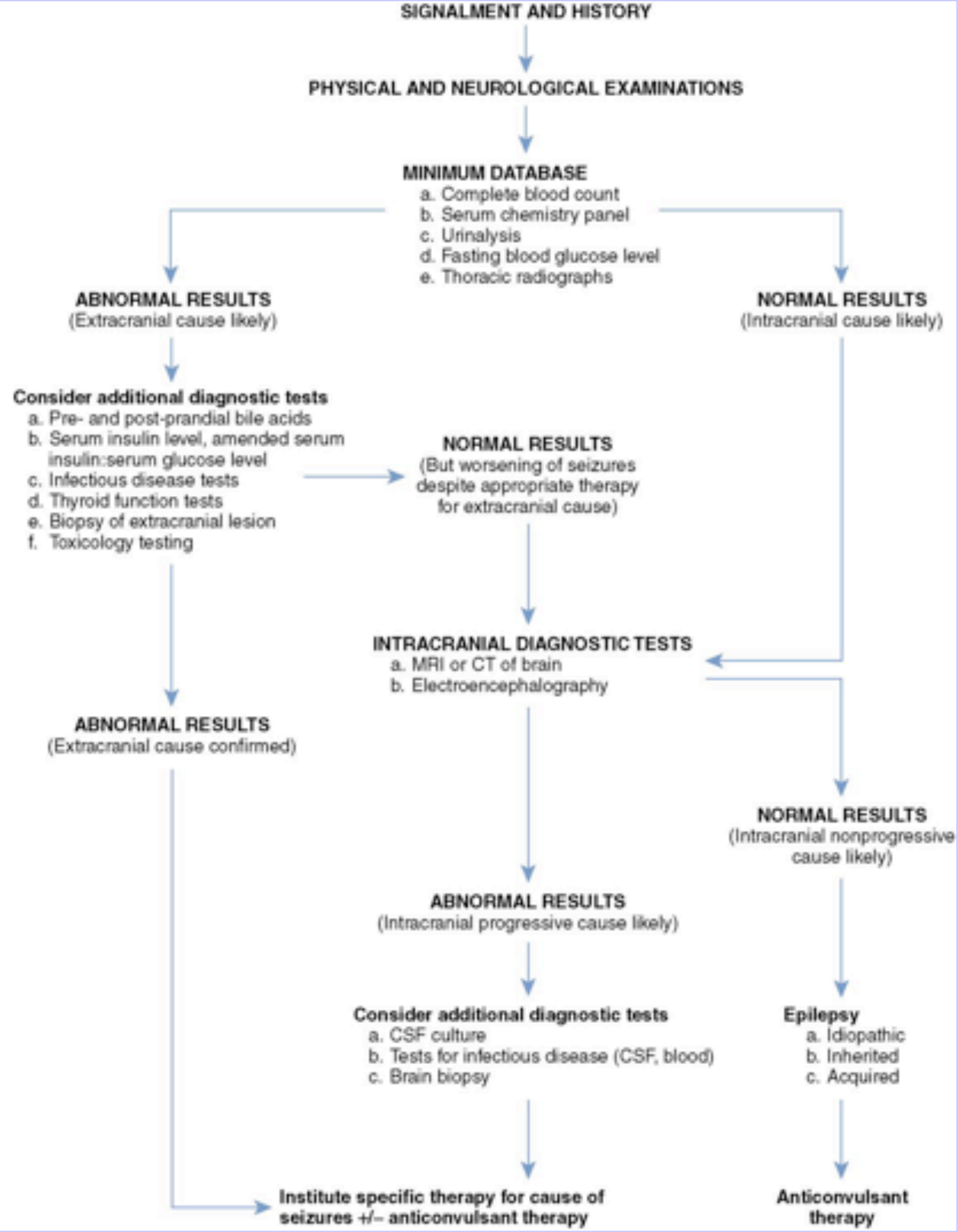
It is essential to distinguish between extracranial and intracranial (progressive and nonprogressive) diseases that cause seizures. Therapy for extracranial and progressive intracranial diseases requires not only control of seizures, but also therapy for the underlying disease.

98.6

DIAGNOSTIC PLAN

A seizure disorder is essentially a manifestation of an underlying disease; therapy is most effective when the underlying disease is diagnosed and treated. Therefore an accurate diagnosis should be established in a timely manner. In some animals an underlying cause may not be identified, as with idiopathic epilepsy. A complete history, physical examination, and neurologic examination should be done in all animals with a seizure disorder (Figure 98-1).

Figure 98-1 Diagnostic approach to seizure disorders in dogs and cats. *CSF,* Cerebrospinal fluid; *CT,* computed tomography; *MRI,* magnetic resonance imaging.


SIGNALMENT AND HISTORY
PHYSICAL AND NEUROLOGICAL EXAMINATIONS
MINIMUM DATABASE
a. Complete blood count
b. Serum chemistry panel
c. Urinalysis
d. Fasting blood glucose level
e. Thoracic radiographs
ABNORMAL RESULTS
(Extracranial cause likely)
NORMAL RESULTS
(Intracranial cause likely)
Consider additional diagnostic tests
a. Pre- and post-prandial bile acids
b. Serum insulin level, amended serum insulin:serum glucose level
c. Infectious disease tests
d. Thyroid function tests
e. Biopsy of extracranial lesion
f. Toxicology testing
NORMAL RESULTS
(But worsening of seizures despite appropriate therapy for extracranial cause)
INTRACRANIAL DIAGNOSTIC TESTS
a. MRI or CT of brain
b. Electroencephalography
ABNORMAL RESULTS
(Extracranial cause confirmed)
NORMAL RESULTS
(Intracranial nonprogressive cause likely)
ABNORMAL RESULTS
(Intracranial progressive cause likely)
Consider additional diagnostic tests
a. CSF culture
b. Tests for infectious disease (CSF, blood)
c. Brain biopsy
Epilepsy
a. Idiopathic
b. Inherited
c. Acquired
Institute specific therapy for cause of seizures +/– anticonvulsant therapy
Anticonvulsant therapy

98.6.1 History

A complete general history should be obtained from the owner, as well as a specific seizure history: age at onset, frequency, and description of seizures, behavior between seizures, and temporal associations (e.g., associated with eating or not eating). A videotape of a seizure may be useful, particularly if the owner's description is insufficient.

98.6.2 Age and Breed

The age at onset is necessary to determine the most likely cause of a seizure disorder. Dogs 5 years and older usually have an acquired seizure disorder, such as a primary brain tumor. The breed is important, because inherited epilepsy is reported in certain breeds such as Beagles, German Shepherds, Poodles, and others.[17] Some breeds may have a higher prevalence of intracranial tumors (Boxers) or inflammatory disease (Maltese dogs).

98.6.3 Physical Examination

A complete physical examination should be done in all animals with seizures, to diagnose systemic problems or local problems (e.g., skull mass) that may affect the brain.

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98.6.4 Neurologic Examination

A complete neurologic examination should be done in all animals with seizures. In animals with inherited or idiopathic epilepsy, neurologic examination findings between seizures most often are normal. Dogs and cats with extracranial or progressive intracranial disease may have neurologic abnormalities between seizures.

Animals may be abnormal neurologically for days after a seizure. Therefore multiple, serial neurologic examinations may be necessary in some animals after a seizure, before neurologic deficits are attributed to extracranial or progressive intracranial disease.

98.6.5 Minimum Database

A minimum database (complete blood count, serum chemistry panel, 24-hour fasting blood glucose, urinalysis) should be done on admission in all animals with seizures. In some animals, serum triglycerides and preprandial and postprandial bile acid levels should be obtained to evaluate the possibility of a portosystemic shunt and hypertriglyceridemia. If systemic disease or intracranial disease is suspected, thoracic radiography and abdominal ultrasonography should be performed to further screen for neoplastic and infectious disease.

98.6.6 Diagnostic Tests for Intracranial Disease

Further investigation of intracranial diseases, including electroencephalography (EEG), MRI, CT, CSF analysis, biopsy (for cytology, histopathology, or both), and serology, may be indicated after a minimum database is completed.

EEG is useful in some animals. When a seizure disorder is suspected, abnormal EEG findings may help to distinguish the presence of seizures from other paroxysmal nonseizure events. EEG may help the clinician to evaluate anticonvulsant therapy, particularly in a patient undergoing treatment for SE, because the external manifestations of seizures may be abolished by drugs.[20] In the future, EEG may be useful in the classification of canine and feline seizure disorders.

MRI is preferred over CT imaging, unless acute head trauma or an acute intracranial hemorrhage is suspected. MRI and CT imaging are noninvasive, and probably yield the most diagnostic information with respect to location and extent of disease in animals with progressive intracranial problems. The results of advanced imaging may help to define a cause of the seizure disorder.

Ideally CSF is collected after MRI or CT imaging has been done. Usually CSF is collected from the cisterna magna (see Chapter 105, Cerebrospinal Fluid Sampling). Because there is risk to the patient undergoing CSF puncture, CSF is not collected in all animals with intracranial disease (see Chapter 100, Intracranial Hypertension). Usually CSF analysis results are supportive of a diagnosis, rather than providing a definitive diagnosis. However, CSF occasionally provides diagnostic information with some infections (e.g., *Cryptococcus neoformans,* bacteria), and with some neoplasms (e.g., lymphoma), and is therefore an essential part of an intracranial workup in most animals.

98.7 TREATMENT PLAN

Regardless of the underlying cause, seizure control is based on selection and administration of an appropriate anticonvulsant drug. Underlying disease, if present, should be treated concurrently. Adverse effects may limit the usefulness of an anticonvulsant drug; therefore knowledge of the mechanisms of action and drug interactions are essential. Selection of an anticonvulsant drug should be based on results of pharmacokinetic studies in the species in which the drug is intended to be used.

The ultimate goal of anticonvulsant therapy is to eradicate all seizure activity; however, this goal rarely is achieved. A more realistic goal is to reduce the severity, frequency, and duration of seizures to a level that is acceptable to the owner, without intolerable or unacceptable adverse effects on the animal. A very general guideline is to consider anticonvulsant drug therapy when the seizure frequency is greater than once every 6 weeks.

Immediate, short-term (acute) anticonvulsant therapy is required to manage SE, cluster seizures, and seizures resulting from some toxicities. Chronic (or maintenance) anticonvulsant therapy is used to manage epilepsy. Seizure control with anticonvulsant drugs is most effective when started early in the course of a seizure disorder, because each seizure may increase the probability of additional seizures secondary to effects such as kindling and mirror focus development.

98.7.1 Status Epilepticus

In SE, the goal of therapy is to stop the seizure as soon as possible. In veterinary medicine, EEG monitoring is not routine in the intensive care unit, so effectiveness of SE therapy is evaluated by the cessation of the outward physical manifestations of a seizure. Therefore, in some animals, although there are no obvious clinical signs of SE, the brain may still have ongoing seizure activity that may negatively affect outcome. As with many disorders in veterinary medicine, there are no controlled clinical trials that may be used to guide therapy. Therefore recommended treatments are guidelines only (Table 98-1).

Treatment should be divided into the (1) immediate emergency evaluation and treatment (such as airway, breathing, cardiovascular function, body temperature, glucose concentration, and blood pressure) (see Chapter 2, Patient Triage) and (2) pharmacologic treatment (see Table 98-1). Animals that are admitted in SE or with cluster seizures, may have cerebral edema, and mannitol administration should be considered (see Chapter 100, Intracranial Hypertension).

98.7.2 Pharmacologic Therapy for Status Epilepticus

98.7.2.1 Benzodiazepines

Diazepam is the first-line agent of treatment of dogs and cats with SE. It is lipid soluble and enters the brain rapidly when given intravenously, intranasally, or per rectum. It binds to the GABA receptor and enhances neuronal hyperpolarization, reducing neuronal firing. The duration of action is short, so a maintenance anticonvulsant (such as phenobarbital) should be administered concurrently, to avoid recurrence of seizures or SE when diazepam levels in the brain decrease. For animals not currently receiving phenobarbital, a loading dosage is administered. Owners may administer PR diazepam to their animals. Midazolam is a water-soluble benzodiazepine and may be used to manage SE. Although the IV route is preferred, midazolam may be given IM if IV access cannot be obtained.

Table 98-1 Anticonvulsant Drugs for Status Epilepticus in Dog and Cats

Drug	Dosage	Comments
Diazepam (first-line)	*IV bolus:* 0.5 to 1 mg/kg may be repeated 2 to 3 times *CRI:* 0.5 to 1 mg/kg/hr *Per rectum:* 0.5 to 1 mg/kg (2 mg/kg if receiving concurrent phenobarbital)	IV injections and infusions should be administered into a central vein
Phenobarbital (maintenance anticonvulsant: use concurrently with diazepam)	2 to 4 mg/kg IV q20-30 min to a total of 18 to 20 mg/kg	Administer concurrently with diazepam to prevent recurrence of seizures once diazepam levels fall in the brain This dose may be repeated every 20 to 30 minutes until a cumulative dosage of 18 to 20 mg/kg has been given Once seizures are controlled a maintenance dosage of phenobarbital is used (3 to 5 mg/kg IV or IM q12h for 24 to 48 hours). Oral anticonvulsant therapy should be resumed or initiated every 12 hours as soon as the animal is able to swallow
Pentobarbital (second-line)	6 to 15 mg/kg IV slow bolus, followed by a CRI of 0.5 to 2 mg/kg/hr to effect	Strict monitoring of physiologic parameters is required
Propofol (third-line)	2 to 8 mg/kg slow IV bolus, given as 25% of the total dose every 30 seconds until desired effect achieved	CRI should be considered (0.1 to 0.4 mg/kg/min) Strict monitoring of physiologic parameters is required (may stop overt manifestations of seizures, but may not stop seizure activity)

CRI, Constant rate infusion; *IM,* intramuscular; *IV,* intravenous.

If SE continues or further seizures occur, additional boluses of diazepam may be given, or a constant rate infusion (CRI) of diazepam may be used. If the SE does not stop, or recurs multiple times, then barbiturates (pentobarbital) are used. The dosage of phenobarbital should be reviewed at this point in time, to ensure that an adequate dose has been administered.

98.7.2.2

Barbiturates

Barbiturates potentiate the action of GABA by interfering with sodium and potassium transmission in the neuronal membrane. Because the half-life of most drugs used to manage SE is short, a maintenance anticonvulsant *must* be part of the treatment regimen. Phenobarbital is the most commonly used maintenance anticonvulsant in dogs with SE because it can be given intravenously.

Pentobarbital is used as a second-line drug if benzodiazepines fail, but it has a limited anticonvulsant effect. Pentobarbital is administered as a bolus, followed by a CRI. Pentobarbital may cause sedation, respiratory depression, hypotension, and death. Animals that are heavily sedated or anesthetized should be intubated so that an open airway is maintained. Other physiologic parameters (such as heart rate, blood pressure, oxygenation, etc.) should be monitored regularly or continuously. Therefore the dosage should be titrated carefully to stop or reduce the motor activity from the seizure, but to avoid anesthesia if possible. During recovery, it may be difficult to determine if the animal is recovering from the pentobarbital or is still having seizures.

98.7.2.3 Propofol

Propofol is a rapid-acting, lipid soluble general anesthetic agent. It is a third-line drug for the management of SE in dogs and cats. The anticonvulsant effect of propofol is likely due to its GABA agonist activity.[21] There are case series describing its use in animals and humans with SE.[21,22] However, propofol use is controversial, because seizures have been associated with its use in humans[23] and in a dog.[24] In one study, humans with SE who were treated with propofol had a higher mortality rate than those treated with midazolam.[22]

98.7.3 Chronic Seizure Disorders

Successful anticonvulsant therapy depends on the maintenance of plasma concentrations of appropriate anticonvulsant drugs within a therapeutic range defined for the species in which the drug is to be administered. Therefore anticonvulsant drugs that are eliminated slowly should be employed. The elimination half-life of anticonvulsant drugs varies considerably between species. Few anticonvulsant drugs used in humans are suitable for use in dogs and cats, largely due to species differences in pharmacokinetics. Pharmacokinetic data for and clinical experience with many anticonvulsant drugs are lacking in cats. Selection should be based on the known pharmacokinetic properties of a drug in the species in which it is to be administered (see Chapter 186, Anticonvulsants).

Phenobarbital and bromide are the first-line of anticonvulsant drugs recommended for chronic seizure disorders in dogs. Phenobarbital is the first-line anticonvulsant in cats.

98.8 SUGGESTED FURTHER READING*

SW Bateman, JM Parent: Clinical findings, treatment, and outcome of dogs with status epilepticus or cluster seizures: 156 cases (1990-1995). *J Am Vet Med Assoc*. **215**, 1999, 1463, *One of the few retrospective studies on SE and cluster seizures in dogs. Patient outcome discussed.*

RA LeCouteur, G Child: Clinical management of epilepsy of dogs and cats. *Probl Vet Med*. **1**, 1989, 578, *A thorough, well written review discussing clinically important aspects of epilepsy in dogs and cats.*

MD Lorenz, JN Kornegay: Seizures, narcolepsy and cataplexy. In MD Lorenz, JN Kornegay (Eds.): *Handbook of veterinary neurology*. ed 4, 2004, Saunders, St Louis, *Clinically useful chapter that includes many relevant tables (such as breeds with primary generalized epilepsy).*

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* See the CD-ROM for a complete list of references

99 Chapter 99 Spinal Cord Injury

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99.1 KEY POINTS

- Spinal cord trauma may result from contusion, compression, or ischemia, or any combination of these events.
- Any animal with suspected spinal cord instability or fractures should be restrained on a flat board or in a small cage until further diagnostic tests are performed.
- An accurate history and lesion localization will lead to a reliable list of differential diagnoses.
- Localization of a lesion should be identified as upper motor neuron (UMN), lower motor neuron (LMN), or a combination of both (i.e., LMN to the thoracic limbs and UMN to the pelvic limbs).
- Prognosis for recovery ranges from excellent to grave, and time is the only certain determinant of the extent of return of function.
- Loss of deep pain for more than 12 to 24 hours following injury and severe luxation or displacement of vertebral bodies carry poor to grave prognoses.

99.2 INTRODUCTION

Injury to the spinal cord is common in domestic animals and may result from vascular, infectious, inflammatory, degenerative, neoplastic, and/or traumatic processes. Animals with disease of the spinal cord may present with only a focal area of spinal pain or with anesthesia and paralysis at the level of and caudal to the lesion. Signs of neurologic dysfunction that fall between these two extremes include spinal ataxia, limping or leg-carrying lameness (a "root signature"), walking paresis, and nonwalking paresis. Animals should be evaluated and their deficits graded using one of several scoring systems[1] (Table 99-1).[2]

This chapter will focus on traumatic spinal cord injuries, including intervertebral disk herniation, and will mention only briefly some other causes of spinal cord disease. It is imperative that the emergency veterinarian be able to recognize neurologic dysfunction, accurately localize the lesion, generate a list of differential diagnoses, perform appropriate diagnostic testing to obtain a definitive diagnosis, institute therapy, and recognize the prognosis of injuries to the spinal cord.

Table 99-1 Neurologic Scoring System

Neurologic Grade	Neurologic Description
Grade 1	No deficits
Grade 2	Paresis, walking
Grade 3	Paresis, nonambulatory
Grade 4	Paralysis
Grade 5	Paralysis, no deep pain

99.3 PATHOPHYSIOLOGY

There are two stages by which the spinal cord is damaged following trauma. Initially there is primary tissue damage from direct mechanical disruption, followed by secondary damage via biochemical and vascular events.[3] When cellular membrane integrity is disrupted, a complex cascade of biochemical reactions is initiated, including the release of excitotoxic amino acids, free fatty acids, oxygen free radicals, and vasoactive agents. N-methyl-D-aspartate (NMDA) receptors are activated, and voltage-sensitive calcium and sodium channels open.[4] These membrane changes result in increased intracellular calcium and sodium, decreased intracellular potassium, and increased extracellular potassium. In addition to changes in ionic concentrations, a decrease in blood flow occurs as a result of direct mechanical compression and/or loss of autoregulation, vasospasm, and hemorrhage, leading to spinal cord ischemia.[3,4] Ischemia results in cytotoxic edema, axonal degeneration, demyelination, abnormal impulse transmission, conduction block, and cell death.[3,4]

99.4 LOCALIZATION

When the animal is presented to the veterinarian, a thorough history should be recorded. If a fracture or luxation is suspected, the goal should be to decrease activity that could further damage the spinal cord. A nonambulatory animal can be placed on a flat board and strapped down. Because some animals object to this, sedation may be required. For an ambulatory animal, placement in a small cage to restrict activity may be all the animal will tolerate. When external trauma to the spinal cord is due to a motor vehicle accident, a fall from a height, or a severe bite wound, it may be necessary to radiograph the entire spinal column immediately following only a limited general and neurologic examination.

A complete neurologic examination should be performed unless it is likely to further injure the patient. The goal of the examination is to identify neurologic dysfunction. Interpretation of the neurologic examination allows the clinician to localize the site of spinal cord injury, because specific signs of dysfunction are seen with injury to certain regions of the spinal cord. For localization of lesions, the spinal cord is often divided into five regions, with disease of each region resulting in a characteristic group of signs. These regions include cervical cord segments one through cervical five (C1-C5), cervical six through thoracic two (C6-T2), thoracic three through lumbar three (T3-L3), lumbar four through sacral one (L4-S1), and sacral one through sacral three (S1-S3). It is important to remember that only spinal cord segments C1, C2, and the last thoracic and first two lumbar segments are located in the vertebral body with the same vertebral number in the dog.[5] More caudally along the spine, the spinal cord segments lie in the spinal canal cranial to the vertebrae with the same number.[6] The presence of spinal cord segments within vertebral bodies of different numbers is important to consider when evaluating images of the spine, particularly in the lower lumbar spine where, for example, spinal cord segments L7, S1, S2, S3, and Cd1 may all be present within the fifth lumbar vertebral body.[7]

If there is no suspicion of a spinal fracture or luxation, the examination should begin with gait analysis. The thoracic and pelvic limbs should be evaluated separately. First, the presence or absence of proprioceptive (spinal) ataxia should be determined. Spinal ataxia is recognized by incoordination that is characterized by an increased stride length, dragging or scuffing the toes, walking on the dorsum of the paw, or crossing over of the limbs. At the same time, the animal is evaluated for paresis (incomplete paralysis often recognized by inability to support weight fully while standing or walking, shuffling of the paws, or trembling when bearing weight) or paralysis (loss of the voluntary ability to move a body part) of one or multiple limbs. Posture is assessed by noting the position of the head and limbs when the animal is at rest and when walking. Once this portion of the examination is completed, postural reactions (replacement of a knuckled over paw, hopping, placing, wheelbarrowing, extensor postural thrust, hemi-standing or hemi-walking) and segmental reflexes (stretch reflexes [extensor carpi radialis, triceps, biceps, quadriceps, cranial tibial, and gastrocnemius] and withdrawal reflexes) should be evaluated. Assessment for the presence of muscle atrophy, sensation (including spinal or limb pain), and normal mental status and cranial nerve function should be performed.

Signs of dysfunction of each of the five the spinal cord regions, beginning caudally and moving cranially, are discussed next.

99.4.1 Spinal Cord Segments S1-S3

The sacral spinal cord segments give rise to the lower motor neurons (LMNs) and sensory fibers that contribute to the sciatic, pelvic, pudendal, and perineal nerves and also connect the caudal spinal cord segments to the spinal cord. General signs of LMN dysfunction are flaccidity, diminished segmental reflexes, and rapidly progressing muscle atrophy (1 to 2 weeks). LMN signs associated with injury to S1-S3 spinal cord segments include paresis/paralysis of the sciatic nerve, anal sphincter, and bladder. If nerve dysfunction is present, the paws of the pelvic limbs may shuffle when walking, a plantigrade posture may be evident (i.e., tarsocrural joint in close proximity to the ground), the knuckled-over paw may fail to be replaced, and the segmental reflexes (i.e., cranial tibial, gastrocnemius, and withdrawal of the distal limb) may be decreased. Note that the femoral nerve is spared with an injury to this area, and therefore the withdrawal will not be completely absent, but instead will manifest with coxofemoral joint flexion without flexion of the tarsocrural joint. Denervation of the anal sphincter and bladder will result in decreased anal sphincter tone and a flaccid bladder. The animal may exhibit fecal and/or urinary incontinence. Additionally, the ability to wag the tail volitionally will be lost (with damage to the caudal spinal cord segments, flaccid paralysis of the tail will result). Sensation may be diminished to the perineum, tail, and lateral and caudal skin of the distal pelvic limbs.

99.4.2 Spinal Cord Segments L4-S1

Spinal cord segments L4-S1 include the lumbar intumescence and give rise to the spinal nerves that contribute to the femoral, obturator, sciatic, pelvic, and pudendal nerves.[2] A lesion of L4-S1 may show dysfunction of the pelvic limbs, tail, and anus with normal thoracic limb function. The pelvic limb gait may be short strided and the paws may shuffle as seen with an S1-S3 lesion. Paresis or paralysis may result in a plantigrade stance or inability to stand or support weight. Other signs include absent to decreased pelvic limb postural reactions, absent to decreased segmental reflexes (femoral, craniotibial, gastrocnemius, perineal, and withdrawal), decreased pelvic limb and anal sphincter tone, urine dribbling, a large flaccid bladder, fecal incontinence, and muscle atrophy of the limbs (if the injury is not acute). Sensation may be decreased at the level of and caudal to the lesion.

99.4.3 Spinal Cord Segments T3-L3

A T3-L3 lesion will result in so-called upper motor neuron *signs* caudal to the level of the lesion. The UMN system originates in the cerebral cortex and brain stem, is confined to the central nervous system, and terminates on the LMN. Strictly defined, the UMN is a *premotor neuron,* because it results in movement and muscle tone only through its actions on the LMN.[8] Diminished UMN influence can result in paresis or paralysis, spasticity, exaggerated segmental reflexes, crossed extensor reflex, and diminished to absent postural reactions. These signs are restricted to the pelvic limbs in animals with a T3-L3 lesion. Additionally, urinary retention, a moderate-sized firm bladder, and fecal incontinence (despite normal anal tone) may occur.

A T3-L3 lesion may also result in incoordination of the pelvic limbs characterized by crossing over of the limbs, increased stride length, abduction or circumduction, or walking on the dorsal surface of the paw. These signs are recognized as proprioceptive (spinal) ataxia and are due to dysfunction of ascending proprioceptive tracts.

Lesion localization can be made more precisely by evaluating the cutaneous trunci reflex and assessing the animal for spinal pain. This cutaneous trunci reflex is tested by pinching the skin lateral to the dorsal midline from the thorax to the level of the L5 vertebral body and observing the movement of the cutaneous trunci muscle. Abnormalities in this reflex will be seen as a lack of muscle movement that is caused by the interruption of sensory input from the stimulated dermatome. The sensory nerve from the dermatome being pinched enters the spinal cord approximately two vertebrae cranial to the level of the stimulated skin. Therefore absence of a cutaneous trunci reflex when the skin is pinched at the level of the L3 vertebral body is consistent with a lesion of the spinal nerves or spinal cord at approximately the L1 vertebral body. If the animal also appears to be in pain when pressure is placed on the L1 vertebral body would also be consistent with a lesion at this location.

A T3-L3 lesion can also result in increased tone to the thoracic limbs. This so-called *Schiff-Sherrington phenomenon* results from a lack of ascending input to the thoracic limbs and originates from originating from neuronal cell bodies of the border cells in the lumbar spinal cord. Border cells are responsible for tonic inhibition of extensor muscle α-motor neurons in the cervical intumescence.[4] Increased thoracic limb tone caused by the Schiff-Sherrington phenomenon is not accompanied by proprioceptive deficits or deficits in voluntary motor function.

99.4.4 Spinal Cord Segments C6-T2

The cervical intumescence gives rise to spinal nerves that make up the subscapular, suprascapular, musculocutaneous, axillary, radial, median, and ulnar nerves.[2] A lesion in the C6-T2 region will cause UMN signs to the pelvic limbs (spastic paresis/paralysis, exaggerated segmental reflexes, and diminished to absent postural reactions) and LMN signs to the thoracic limbs (short-strided gait, flaccidity, diminished segmental reflexes, diminished to absent postural reactions, and rapidly progressing muscle atrophy). The animal may also limp or carry a thoracic limb because of nerve root compression (root signature). This neuropathic lameness often confused with lameness due to orthopedic disease. A neurogenic cause of the lameness can frequently be ascertained by identifying proprioceptive deficits, nonuniform muscle atrophy over the limb or by electrodiagnostic testing. Additional signs may include absence of the cutaneous trunci reflex, Horner syndrome, and decreased thoracic wall movement when breathing. The cutaneous trunci reflex may be absent (unilateral or bilateral) as a result of damage to the LMNs that contribute to the lateral thoracic nerve. Horner syndrome (miosis, ptosis, and enophthalmos) results from damage to the sympathetic fibers that leave the spinal cord at this level. Decreased movement of the thoracic wall with respiration occurs because of the inability of the brain stem to control intercostal nerve function. If only the phrenic nerve is functioning properly, diaphragmatic (abdominal) breathing may be seen.

A characteristic gait can occur with lesions of the C6-T2 spinal cord segments. The pelvic limbs may show spinal ataxia and the thoracic limbs a short-strided gait. This mix of signs is often referred to as a *two-engine gait.*

99.4.5 Spinal Cord Segments C1-C5

Lastly, a lesion of spinal cord segments C1 to C5 may show UMN signs in both the pelvic and thoracic limbs. Respiration may be shallow or absent because of the loss of phrenic and intercostal nerve function. Spinal ataxia of all limbs is seen, characterized by a long-strided or “floating” thoracic and pelvic limb gait.

99.4.6 Spinal Shock

In animals examined soon after spinal cord injury, a phenomenon called *spinal shock* may be present, leading to inaccurate neurolocalization. Spinal shock is a profound depression of segmental reflexes caudal to a lesion, despite reflex arcs remaining physically intact. In dogs, these signs often occur transiently, with evidence of areflexia lasting up to 12 to 24 hours after an injury.[9] This exemplifies the importance of performing serial neurologic examinations after a spinal cord injury to ensure accurate neurolocalization.

99.5 DIAGNOSIS

Once the neurologic examination is completed and a lesion or lesions are localized, a list of differential diagnoses should be formulated.[10] Differential diagnoses for spinal cord lesions include trauma (fracture, luxation, subluxation, bruise, intervertebral disk herniation), vascular diseases (hemorrhage, fibrocartilaginous emboli, infarct), neoplasia, malformations (atlantoaxial subluxation, arachnoid cysts, syrinx) and, less commonly, infectious (toxoplasmosis, Rocky Mountain spotted fever, neosporosis, ehrlichiosis, feline infectious peritonitis, fungal, bacterial), inflammatory (granulomatous meningomyelitis), and degenerative diseases (degenerative myelopathy). History, patient age and breed, onset and progression of signs, and presence or absence of pain help to generate a likely list of differential diagnoses (Table 99-2).

At this point, additional diagnostic tests should be performed. Plain radiographs of the spine, including lateral and ventrodorsal (or dorsoventral) views, should be obtained. These radiographs can show obvious fractures, displacement of vertebrae, narrowing of the intervertebral disk space, articular facets or intervertebral foramen, lytic lesions or sclerotic lesions. If available, myelogram, magnetic reasonance imaging, computed tomography, and cerebrospinal fluid analysis may be required. Thoracic and abdominal radiographs and/or ultrasonography may also be indicated based on the animal's clinical signs or history.

99.6 TREATMENT

Emergency treatment of spinal cord injury may vary depending on the diagnosis. For all acute spinal cord injuries, intravenous fluid therapy is indicated because of presumed compromise of spinal cord vasculature that inhibits the normal autoregulation of arteriolar blood flow (see Chapters 64 and 65, Daily Intra-venous Fluid Therapy and Shock Fluids and Fluid Challenge, respectively). As a result, blood flow to the damaged spinal cord is dependent on mean arterial blood pressure, so cardiovascular stability must therefore be maintained.[3,4]

If a fracture or displacement of the spine is detected, the animal should be heavily sedated or anesthetized in order to place a splint aimed at immobilizing the spine. In the case of a cervical fracture or displacement, the splint should be placed on the ventral aspect of the neck, extending from the rostral portion of the mandible to the manubrium of the sternum. Bandaging material can be used to hold the splint in place and should start just caudal to the ears and extend beyond the caudal aspect of both scapulas. In the case of a thoracic or lumbar fracture or displacement, a V-shaped splint should be placed over the spine and secured firmly with bandage material. It is important to avoid placing the splint so tightly that respiration is impaired.

If the injury requires surgery and consent has been given by the owner, the animal should be referred to an experienced surgeon. Surgical fixation has been indicated as the treatment of choice in animals with atlantoaxial subluxation to prevent recurrence of signs.[11] Fractures can be complicated and, depending on the location of the fracture, surgery may or may not be indicated. If the fracture incorporates the articular facets, the vertebral body, or both, internal fixation is recommended.[12] Luxations or subluxations that have compromised the ventral buttress (vertebral body, dorsal and ventral longitudinal ligaments, and intervertebral disks) are susceptible to rotation and require surgical repair to inhibit this movement.[12] However, for animals in which the neurologic status is not deteriorating, external support and strict rest are the treatments of choice for displaced or unstable fractures of the cervical spine.[13] This is due to the high incidence of mortality (approximately 40%) associated with surgical intervention for cervical fractures.[13] Intervertebral disk disease resulting in moderate to severe neurologic deficits, recurrent episodes, and episodes unresponsive to medical treatment should be treated with surgical decompression.

Pain control for animals with spinal cord injury often requires pure opioid agonists (fentanyl, hydromorphone, oxymorphone, or morphine) or a partial opioid agonist (buprenorphine). If these medications are used, the patient should be closely monitored for respiratory depression (see Chapter 164, Analgesia and Constant Rate Infusions).

Treatment for spinal cord edema and lipid peroxidation is a controversial subject. Methylprednisolone sodium succinate at 30 mg/kg IV has been shown to improve neurologic outcome in humans if given within 8 hours of the injury,[14] although similar studies have not been performed in the dog or cat. Subsequent doses of methylprednisolone sodium succinate at 10 mg/kg IV can be given for 24 hours post injury.[9] Gastrointestinal protectants such as histamine-2 blockers (e.g. famotidine) can be given for 24 to 48 hours post injury to decrease the likelihood gastric irritation or ulcers induced by spinal cord injury and steroid administration (see Chapter 181, Gastrointestinal Protectants).

Table 99-2 Differential Diagnoses for Spinal Cord Lesions Based on Signalment, History, and Physical Examination

	Young	Old	Acute Onset	Insidious Onset	Nonprogressive	Progressive	Nonpainful	Painful
Trauma	++	+	+	–	+	–	–	+
IVDD type 1	+	+	+	–	–	+	–	+
IVDD type 2	–	+	–	+	–	+	–	±
Vascular disease	+	+	+	–	+	–	+	–
Infectious and inflammatory disease	++	+	+	–	–	+	±	±
Degenerative disease	–	+	–	+	–	+	+	–
Anomalous or malformation	+	–	+	+	+	–	++	±
Neoplastic disease	+	++	+	+	–	+	±	±

IVDD, Intervertebral disk disease.

++, More likely; +, yes; –, no; ±, sometimes.

99.7 PROGNOSIS

The prognosis for animals with spinal cord injury is extremely variable and difficult to predict. Many factors play a role in outcome including age, size, and breed of the animal, etiology, onset of clinical signs, severity of signs, and location of disease. Animals with cervical spinal cord injury caused by trauma, atlantoaxial subluxation, and intervertebral disk herniation have differing prognoses. Dogs with cervical spine trauma have been reported to have a good prognosis (recovery rate of 82%) if the animal does not suffer from acute respiratory failure.[13] Atlantoaxial subluxations resulting in severe neurologic deficits that are treated conservatively (i.e., splint stabilization) have been reported to have a good to guarded prognosis for recovery (good outcome in 62.5% of dogs), but approximately 25% relapse at a later date.[11] Surgical stabilization has also been reported to have a good to guarded prognosis for recovery,[11] with success rates ranging from 61% to 91%.[16-18] Cervical intervertebral disk herniation (IVDH) treated via ventral slot in animals with tetraparesis or tetraplegia was present before surgery has been reported in one study to have a 56% chance of recovery in 1 to 6 weeks. Animals with only pelvic limb paresis had a 75% chance of recovery in 3 to 8 weeks.[15] Another study reports a better outcome in patients with high cervical intervertebral disk herniation (C2-C3 and C3-C4), with long-term resolution after ventral decompression seen in 66% of dogs. However, in animals with caudal cervical sites of intervertebral disk herniation (IVDH) (C4-C5, C5-C6, and C6-C7) only 21% had long-term resolution of signs.[19] The most common postoperative complications include vertebral instability and subluxation. Another important complication is hypoventilation requiring ventilatory support. This was seen in 4.9% of dogs that underwent surgery for cervical spinal cord disorders.[21]

Thoracolumbar spinal cord injuries have also had varying reports of success. In a study of nine cases of traumatic injuries (e.g., trauma caused by car accidents or being dropped) that resulted in the loss of deep pain sensation, none of the dogs regained deep pain sensation with treatment (six treated conservatively and the remaining three treated surgically), but two did regain the ability to walk (spinal walking).[22] Another report indicated that loss of deep pain sensation due to thoracolumbar luxation or fracture resulted in a less than 10% recovery rate (i.e., motor ability).[2,23] A loss of deep pain for more than 12 to 24 hours following injury and severe luxation or displacement of vertebral bodies also carries a poor to grave prognosis.[20] Overall, the prognosis for recovery after trauma to the thoracolumbar spinal cord that results in the loss of deep pain sensation is extremely grave.

In cases of thoracolumbar disk herniation, many studies have revealed varying rates of recovery (25% to 76%) for dogs that did not have deep pain sensation in the pelvic limbs.[17,24-28] In contrast, the recovery rate for dogs that have retained deep pain sensation in the pelvic limbs is very good and is reported to be in the range of 86% to 96%.[27,28]

99.8 SUGGESTED FURTHER READING*

RS Bagley: Spinal fracture or luxation. *Vet Clin North Am Small Anim Pract*. **30**, 2000, 133, *A great chapter discussing clinical assessment and treatment of animals with suspected spinal trauma. Contains great pictures of imaging studies and immobilization techniques, as well as discussions on surgical and nonsurgical treatments and follow-up management.*

NJ Olby: Current concepts in the management of acute spinal cord injury. *J Vet Intern Med*. **13**, 1999, 399, *A great review article discussing the events during lesion development and treatment recommendations after the injury*.

NJ Olby, J Levine, T Harris, et al.: Long-term functional outcome of dogs with severe injuries of the thoracolumbar spinal cord: 87 cases (1996-2001). *J Am Vet Med Assoc*. **222**, 2003, 762, *An article that compares outcomes in dogs with loss of deep pain sensation from traumatic deep pain loss and loss of deep pain from intervertebral disk herniation.*

NJ Sharp, SJ Wheeler: In *Small animal spinal disorders*. ed 2, 2005, Mosby, Edinburgh, *A superior book describing diseases that affect the spinal cord, step-by-step surgical procedures, and prognosis associated with the particular treatments. A book that all veterinarians with a special interest in neurology and neurosurgery should read.*

* See the CD-ROM for a complete list of references

100 Chapter 100 Intracranial Hypertension

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100.1 KEY POINTS

- Intracranial hypertension (ICH) is the persistent elevation of intracranial pressure (ICP) above the normal range of 5 to 12 mm Hg.
- Causes include trauma, hemorrhage, infarction, ischemia, edema, masses, encephalopathy, and status epilepticus.
- ICH develops when the volume of the intracranial contents exceeds the accommodation of compensatory mechanisms.
- ICH damages the brain through its deleterious effects on cerebral blood flow (CBF) and oxygen delivery causing hypoxia, ischemia, and brain herniation.
- The primary treatment goals are maintenance of CBF and tissue oxygenation without causing or worsening ICH.
- Effective management of ICH includes critical maintenance of cerebral perfusion pressure (CPP) and often requires hyperosmolar therapy.

100.2 PHYSIOLOGY OF INTRACRANIAL PRESSURE

100.2.1 Intracranial Fluid Dynamics

The collective volume of intracranial contents is the major determinant of intracranial pressure (ICP). The cranial space may be divided into four distinct physiologic compartments, each with separately regulated water content: blood, cerebrospinal fluid (CSF), intracellular fluid (ICF), and extracellular fluid (ECF).

100.2.2 Cerebrospinal Fluid Flow

Most CSF is formed by ultrafiltration of fluid from the blood vessels of the choroid plexus lining the ventricles and drains into the subarachnoid space, from where it is absorbed. When ventricular pressure is elevated the flow of fluid may be reversed, back into the brain parenchyma.[2] As compensation for intracranial hypertension (ICH), CSF production falls, absorption increases, and a greater volume of CSF is displaced into the spinal subarachnoid space.[1,3]

100.2.3 Brain Water Movement

The blood-brain barrier (BBB) tightly regulates the entry of solutes into the brain but is permeable to water. Changes in effective osmolality across the BBB are accompanied by water movement to equalize osmolality, but at the expense of changes in cell volume. With increases in the osmolality of intravascular fluid or ECF, ICF may shift to the extracellular environment. With persistence of hyperosmolar conditions in the extracellular fluid for many hours, brain cells, having lost volume, will compensate by generating intracellular osmolytes (idiogenic osmoles) to raise the osmotic pull intracellularly and restore cell volume. Breakdown of these idiogenic osmoles occurs over several days. Rapid decreases in ECF osmolality should be prevented, because the intracellular osmolytes may draw water into the cell, causing cell swelling, membrane disruption, and exacerbation of ICH.[4]

100.2.4 Cerebral Blood Flow

The high metabolic demands of the brain require maintaining cerebral blood flow (CBF) in the normal range at all times. CBF is dependent on cerebral perfusion pressure (CPP), which is calculated as mean arterial pressure (MAP) minus ICP[4-6]:

$$\text{CPP} = \text{MAP} - \text{ICP}$$

The volume of blood in the brain (cerebral blood volume [CBV]) is affected by factors that change CBF, such as altered vascular tone, and those that impair venous outflow, such as head-down posture, jugular vein compression, or increased intrathoracic pressure.[1,4,5] Cerebrovascular vasodilation serves to increase CBF and thereby CBV, leading to increased ICP; cerebral vasoconstriction decreases CBF, CBV, and therefore ICP, but may result in hypoxia and neuronal ischemia.[1,4,5]

100.3 INTRACRANIAL PRESSURE

Intracranial pressure ICP is the pressure inside the cranial vault exerted by the tissues and fluids against the encasing bone. Normal ICP in the dog is 5 to 12 mm Hg, similar to that of humans for whom 20 mm Hg is an arbitrary upper limit beyond which treatment for ICH may be instituted[1,3] (see Chapter 209, Intracranial Pressure Monitoring). The upper limit of ICP above which treatment is indicated for ICH has not been defined in dogs and cats. It seems reasonable to utilize the human guidelines for ICH until species-specific information is available.

100.3.1 Homeostatic Responses of the Brain

Three primary homeostatic mechanisms exist to maintain ICP within a range where the brain is functional. These include volume buffering, autoregulation, and the Cushing response.[1,4-6]

100.3.1.1 Volume Buffering

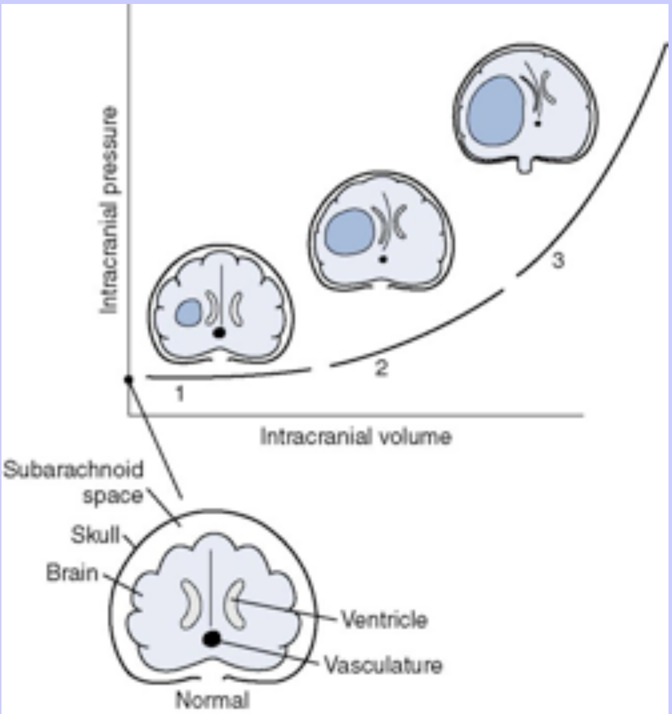
The brain is relatively noncompressible and is encased in bone, causing the volume of the intracranial contents to be fixed. Increase in the volume of one component requires a compensatory decrease in one or more of the others if ICP is to remain unchanged (Monroe-Kellie doctrine). Sources of added volume include hemorrhage, CSF accumulation, vascular congestion, cerebral edema, and decreases in venous outflow (Figure 100-1). Immediate volume buffering responses, specifically displacement of blood and CSF extracranially, are reflected by the pressure-volume curve that relates the temporal change in ICP to expanding intracranial volume.

100.3.1.2 Autoregulatory Mechanisms

100.3.1.2.1 Pressure Autoregulation

Autoregulation of CBF results from a vascular (myogenic) reflex that changes resistance of cerebral arterioles in response to changes in transmural pressure. The purpose is to prevent underperfusion or overperfusion of the brain. Normally this mechanism operates at perfusion pressures between 50 and 150 mm Hg. Outside this range, CBF becomes linear with MAP (Figure 100-2).[1,4,5]

Figure 100-1 Pressure-volume curve. An idealized elastance curve that illustrates changes in intracranial pressure (ICP) accompanying the progressive addition of intracranial volume. First segment: Compliance is high, compensatory mechanisms are functioning well, primarily a result of expansion of the dura mater in the cranial and cervical spinal space, allowing for added volume with no or little increase in ICP. Second segment: As volume is added to the system, displacement of cerebrospinal fluid and blood allow for further volume additions with progressive changes in ICP. Third segment: The vertical portion of the elastance curve shows the high-pressure, low-compliance situation that occurs when the volume buffering capacity is exhausted. Further displacement of intracranial fluids is not possible and addition of more volume causes an exponential rise in ICP. Decompensation is occurring and any volume buffering at this point is due to distention, compression, and eventual herniation of neural tissues.



100.3.1.2.2 Chemical Autoregulation

Chemical regulation of cerebral vascular resistance is influenced by three factors: partial pressure of arterial carbon dioxide ($PaCO_2$), partial pressure of arterial oxygen (PaO_2), and cerebral metabolic rate of oxygen consumption.[1,4,5]

100.3.1.2.2.1 Partial Pressure of Arterial Carbon Dioxide

Cerebral vascular resistance is directly responsive to changes in $PaCO_2$ concentrations, because carbon dioxide combines with water to form hydrogen ions, which when increased in concentration stimulate cerebral vasodilation and when decreased may cause vasoconstriction. Therefore, in the normal brain, hyperventilation decreases $PaCO_2$ causing vasoconstriction, reduced cerebral blood volume, and lowering of ICP.

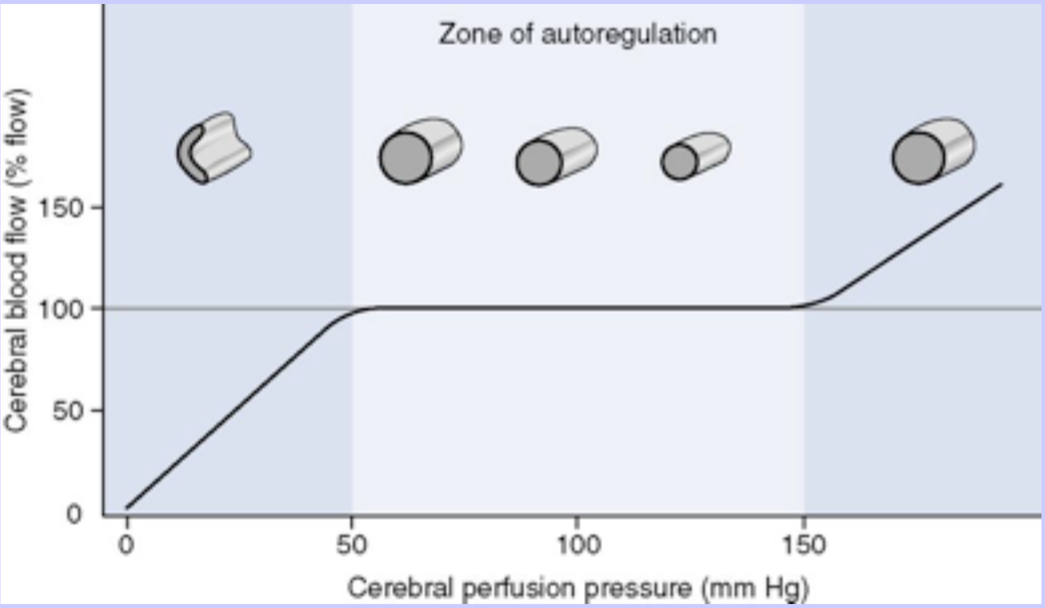
100.3.1.2.2.2 Partial Pressure of Arterial Oxygen

Decreases in PaO_2 cause vasodilation, resulting in increased CBF, CBV, and ICP.

100.3.1.2.2.3 Cerebral Metabolic Rate of Oxygen Consumption

CBF is coupled to local cerebral metabolism. In regions of high cerebral metabolic activity, pH alterations in the perivascular environment will have a direct influence on cerebral vascular tone.
Increased hydrogen ion concentration, as seen with lactic acidosis or accumulation of other acids formed 424
during the course of cerebral metabolism, will cause an increase in CBF. When cerebral metabolic rate of 425
oxygen consumption is decreased, low levels of hydrogen ion concentration will result in decreased CBF locally as a result of arteriolar constriction.

Figure 100-2 Classic cerebral pressure autoregulation curve. Cerebral autoregulation maintains a relatively constant rate of cerebral blood flow across a wide of range of cerebral perfusion pressures as shown (50 to 150 mm Hg). With intact autoregulation, cerebrovascular tone appears to respond to transmural pressure, which is approximately the same as cerebral perfusion pressure. Note the marked rise and fall in cerebral blood flow as cerebral perfusion pressure changes above and below, respectively, the normal limits of autoregulation. With impairment of autoregulation in the injured brain, cerebral blood flow will passively follow systemic arterial blood pressure.



100.3.1.2.2.4

Cushing Response

Autoregulation often is impaired in animals with intracranial disease where pressure autoregulation generally is affected first and chemically mediated regulation is affected more as brain injury progresses. When volume buffering and autoregulatory adjustments are exhausted, ICH will lead to decreased CBF, cerebral ischemia, and accumulation of carbon dioxide. Decreased CBF and elevated carbon dioxide levels can stimulate the release of catecholamines which may cause systemic vasoconstriction and increased cardiac output. Baroreceptors sense this hypertensive state and cause a vagally mediated bradycardia. Hypertension and bradycardia secondary to ICH is known as the *Cushing response*. The catecholamine release also may result in cardiac arrhythmias due to myocardial ischemia, the so-called brain-heart syndrome.

100.4 CAUSES OF INTRACRANIAL HYPERTENSION

In general terms, causes of ICH can be classified as vascular or nonvascular. Vascular mechanisms of ICH include cerebral vasodilation caused by increased $PaCO_2$, distention of cerebral vessels due to loss of vascular tone, or venous outflow obstruction. Nonvascular mechanisms are increased brain water (interstitial edema or intracellular swelling), masses, or obstruction of CSF outflow.

Pressure gradients associated with ICH may result in movement of neural tissues within and between anatomic compartments (brain herniation) that may perpetuate injury and ischemia by distorting or fracturing brain tissue, and by compression and shearing of cerebral vasculature.[1,7]

100.5 CLINICAL ASPECTS OF INTRACRANIAL HYPERTENSION

A complete history and physical examination are essential in the assessment of patients suspected to have ICH. A careful neurologic examination is required for accurate clinical diagnosis, institution of therapy, and determination of a baseline to which results of future examinations may be compared. Aspects of the neurologic examination that are of particular importance include level of consciousness, brain stem reflexes, respiratory pattern, motor responses, abnormal postures, and breathing patterns. Papilledema identified on fundic examination is a reliable sign of ICH.

100.5.1 Level of Consciousness

Four levels of consciousness are recognized:

1 *Alert and responsive:* Normal responses to sensory stimuli; expected behavior

2 *Obtunded (depressed):* Slow or inappropriate response to sensory stimuli

3 *Stuporous (semicomatose):* Generally unresponsive, except to vigorous or painful stimuli

4 *Comatose:* Complete unresponsiveness to repeated noxious stimulation.

The mechanisms responsible for consciousness are located in the rostral brain stem, the ascending reticular activation system (ARAS; reticular formation), and diffusely throughout the cerebrum.

Progression from a higher to a lower level of consciousness often is caused by elevation of ICP. Although focal loss of autoregulation may not be recognized clinically, unconscious animals are likely to have global impairment of autoregulatory responses.[1,4]

100.5.2 Brainstem Reflexes

100.5.2.1 Size and Reactivity of Pupils

The midbrain and efferent parasympathetic fibers of the oculomotor nerve (cranial nerve III; CN III) are responsible for pupillary constriction. In the absence of ophthalmic injury, abnormalities in pupil size or reactivity indicate brainstem dysfunction. Several patterns of pupillary abnormality are commonly recognized in patients with ICH:

1. *Mydriasis* usually denotes a lesion (ipsilateral or bilateral) of the midbrain or the CN III.
2. *Miosis* may occur ipsilateral to severe brainstem injury or as part of Horner's syndrome (ptosis, 425
   enophthalmos, third eyelid protrusion), indicating a lesion affecting the sympathetic pathway to the eye. 426
3. *Severe bilateral miosis* is a sign of acute, extensive brain disturbance and probably occurs as a result of functional disturbance of higher centers, with release of CN III efferents from cerebral inhibition.
4. *Severe, unresponsive bilateral mydriasis* generally indicates a grave prognosis, and it often accompanies brain herniation.

The return of pupils to normal size and responsiveness to light is a favorable prognostic sign.

100.5.2.2 Resting Eye Position, Eye Movements, and Oculovestibular Reflexes

1. Resting eye position and presence of spontaneous nystagmus should be noted. Eye abduction may be caused by medial rectus muscle paresis due to CN III damage. Adduction may be caused by lateral rectus muscle paresis due to abducens nerve (CN VI) damage, or damage to the rostral medulla oblongata or pons.
2. Oculovestibular movements are elicited by moving the head from side to side or vertically. Conjugate oculovestibular movements require integrity of the brainstem pathways from the cranial cervical spinal cord and medulla oblongata rostrally to the nuclei of CN III, CN IV (trochlear nerve) and CN VI, via the medial longitudinal fasciculus. Thus the oculovestibular maneuver is a convenient method for examination of the functional integrity of large areas of the brain stem and the cranial nerves involved in eye movements.

100.5.2.3 Corneal Reflexes

Although evaluation of corneal reflexes alone rarely is useful, findings may corroborate eye movement abnormalities. Touching the cornea with a wisp of cotton should cause bilateral eyelid closure. The corneal reflex may be absent when the afferent trigeminal nerve (CN V), the efferent facial nerve (CN VII), or their reflex connections within the pons and medulla oblongata are damaged.

100.5.3 Respiration

Breathing is regulated principally by respiratory centers in the caudal brain stem between the midpons and cervico-medullary junction. Respiratory patterns have proven useful, but inconsistent, in localizing brain injury.

1. *Cheyne-Stokes respiration* consists of phases of hyperpnea regularly alternating with apnea. Its presence implies a lesion deep in the cerebral hemispheres or in the rostral brain stem.[1]
2. *Central neurogenic hyperventilation* consists of sustained, rapid, fairly deep, and regular respirations at a rate of approximately 25 breaths/min, with hypocapnia. This respiratory pattern may indicate a lesion in the caudal midbrain and pons.[1]
3. *Neurogenic pulmonary edema* may occur almost instantaneously following rostral brain stem injury in the absence of direct pulmonary trauma.[1] ICH occasionally may result in neurogenic pulmonary edema.
4. *Gasping or chaotic respirations* reflect caudal brain stem damage and represent the terminal respiratory pattern of severe ICH. The appearance of, or progression to, abnormal respiratory patterns, strongly suggests that the animal is deteriorating and mandates more aggressive medical therapy or surgery.[1]

100.5.4 Motor Responses

Ataxia and paresis may determined by observing the gait and response to testing of postural reactions. If an animal is non-ambulatory, voluntary movement of the limbs is determined based on response to noxious stimuli.

100.5.5 Posture

Decerebrate rigidity occurs with midbrain lesions and is characterized by unconsciousness, recumbency, opisthotonos, and rigid extension of all limbs. This posture signifies a grave prognosis and must be distinguished from decerebellate posture and the Schiff-Sherrington syndrome, in which extensor rigidity is present in the thoracic limbs but the animal is conscious.

100.6 DIAGNOSIS OF INTRACRANIAL HYPERTENSION

In the absence of direct ICP monitoring, a clinical diagnosis of ICH usually is based on results of serial neurologic examinations. Ultimately, if ICH is not controlled, significant shifts in brain parenchyma will occur, leading to forcible movement of brain tissue, or herniation. CT or MR imaging may be more sensitive than clinical examination in detecting brain herniation in animals. For example, a slow-growing brain tumor may cause significant cerebellar herniation in a patient without clinical signs of ICH.

Brain death usually is indicated clinically by coma, absence of spontaneous respiration, and loss of brain stem reflexes (e.g., fixed, dilated pupils). Additional criteria used in human patients include an isoelectric electroencephalogram and absence of CBF on arteriographic evaluation.[1]

100.7 TREATMENT OF INTRACRANIAL HYPERTENSION

Appropriate treatment of ICH is often more important to the short-term survival of the patient than primary treatment of the underlying brain disease. Treatment goals include reduction of intracranial volume and prevention of secondary brain injury by restoration and maintenance of circulating blood volume, blood pressure, oxygenation, and ventilation[4-6,8] (Box 100-1).

100.7.1 General Supportive Care

The initial step is to recognize and correct life-threatening, nonneural injuries, especially in the case of brain trauma.[8,9] Shock most often is due to tissue damage and blood loss from other organs; intracranial disease alone, including head trauma, rarely results in shock.

100.7.1.1 Prevent Hypoxia

The animal should be placed in an oxygen-rich environment with its head elevated and a clear airway. Oxygen supplementation will not prevent hypercapnia in a hypoventilating animal. Tracheal intubation and mechanical ventilation are indicated in apneic or hypoventilating patients.[8,9]

100.7.1.1.1 Box 100-1 Concepts in Management of Intracranial Hypertension

100.7.1.1.1.1 Reduction of Intracranial Volume

- Reducing brain size and edema
- Reducing CSF volume and obstruction to flow
- Reducing cerebral blood volume
- Reducing the size of pathologic process (tumor, hematoma, inflammation)
- Increasing the space for expansion of structures by decompressive craniectomy

100.7.1.1.1.2 Prevention of Secondary Brain Injury

- Preventing hypoxia
- Preventing hypotension
- Maintaining euvolemia, euglycemia
- Maintaining electrolyte and acid-base balance
- Managing seizures, fever, SIRS, MODS

CSF, Cerebrospinal fluid; *MODS,* multiple organ dysfunction syndrome;

SIRS, systemic inflammatory response syndrome

100.7.1.2 Prevent Hypotension

Prevention and management of hypotension are central to the treatment of ICH; hence, intensive monitoring of arterial blood pressure is essential.[4,8,9]

100.7.2 Guidelines for Specific Therapy of Intracranial Hypertension

After general supportive measures have been completed, medical treatment is instituted to reduce brain edema, decrease ICP, and maintain cerebrovascular perfusion and tissue oxygenation. The patient should be assessed (at least) every 15 to 30 minutes until stabilized. A response to therapy should be seen within 2 hours; if a response does not occur, medical therapy should be reassessed, and surgical therapy considered (Box 100-2).

100.7.2.1 Maintain Adequate Cerebral Perfusion Pressure

Maintenance of adequate CPP is the theoretical basis for managing ICH.[1,10,11] For CPP to remain constant, the MAP must increase when ICP increases. If the ICP cannot be controlled after adequate fluid resuscitation, vasopressors may be considered to increase MAP.[10] However, in the absence of cerebral ischemia, attempts to maintain CPP at over 70 mm Hg with pressors should not be pursued aggressively.[10,11] CPP in dogs and cats ideally is maintained at 50 to 90 mm Hg. When it is not possible to monitor ICP, mean arterial blood pressure should be maintained at or above 80 mm Hg.

100.7.2.2 Decrease Cerebral Venous Blood Volume

Head elevation promotes drainage of venous blood to reduce ICP. Neck wraps, improper positioning of the head and neck, or positive end-expiratory pressure may impair venous drainage, causing an increase in brain volume.

100.7.2.3 Control $PaCO_2$

The most important factor controlling CBF and CBV is $PaCO_2$.[5] Controlled ventilation, used judiciously, can lower ICH by vasoconstriction and reduced CBF. The target $PaCO_2$ is 30 to 35 mm Hg. Lower values may lead to neuronal ischemia and exacerbation of ICH.[5,11,12]

100.7.2.3.1

Box 100-2 Suggested Protocols for Initiating Management for Intracranial Hypertension

100.7.2.3.1.1

Management for ICH

100.7.2.3.1.1.1

All patients with evidence of ICH or at risk of developing ICH

Prevention of hypercapnia with a target $PaCO_2$ of 30 to 35 mm Hg

Oxygen supplementation as needed to maintain a PaO_2 >80 mm Hg

Head elevation (30 degrees) and prevention of jugular compression

Removal of causes of increased intrathoracic pressure

Control of systemic factors

- Prevent hypotension
- Prevent hypoxia
- Prevent electrolyte and acid-base imbalances
- Maintain euvolemia and euglycemia

100.7.2.3.1.1.2

Clinical Evidence of Marked ICH: Deteriorating Neurologic Status

All of the above therapies

Hyperosmolar agents

Ventricular CSF drainage if feasible

100.7.2.3.1.1.3

Clinical Evidence of Severe ICH: Comatose Mental State, or Rapid Neurologic Deterioration

All of the above therapies

Hyperventilation therapy

Barbiturate coma

Decompressive craniectomy

CSF, Cerebrospinal fluid; *ICH,* intracranial hypertension; *$PaCO_2$*, partial pressure of arterial carbon dioxide; *PaO_2*, partial pressure of arterial oxygen.

100.7.2.4 Control PaO_2

CBF begins to increase when PaO_2 falls below 60 mm Hg. However, the brain is even more sensitive to arterial oxygen content. For example, in humans, halving the hematocrit will double the CBF, even if PaO_2 is higher than 60 mm Hg.[5]

100.7.2.5 Reduce Cerebral Edema With Hyperosmolar Fluid Therapy

Reduction of brain water content has long been theorized to be an effective means of controlling ICP. To this end, the misguided practice of dehydrating patients by using diuretics or restricting fluids was used initially to manage ICH. In more recent years, hyperosmolar agents have been used widely.[8,10,11] The patient's fluid and electrolyte balance should be determined before starting hyperosmolar therapy.

100.7.2.5.1 Mannitol

The short-term beneficial effects of mannitol on ICH, CPP, and CBF are widely accepted.[8,10,11,13] Although the mechanism of action is controversial, mannitol probably has two effects: (1) an immediate (within minutes) plasma-expanding effect that reduces blood viscosity, thus increasing CBF and the delivery of oxygen to the brain, and (2) a delayed osmotic effect that occurs 15 to 30 minutes after administration when gradients are established between plasma and cells, causing a reduction in brain water content. An osmotic increase of at least 10 mOsm is thought to be required for this effect to be seen. This delayed effect persists for 1 to 3 hours. It is thought best not to exceed a plasma osmolality of 320 mOsm/kg. However, the authors have routinely used hyperosmolar therapy in animals with blood osmolalities higher than this, without adverse effects, in situations of severe ICH. Strict monitoring and maintenance of fluid and electrolyte balance are essential during mannitol therapy. 427 428

The recommended dosage is 20% mannitol solution 0.5 to 1 g/kg IV over 20 minutes.

Mannitol should be administered as repeated doses, not as a continuous infusion. Dangers of repeated dosage are related to effects on blood volume and electrolytes rather than specific toxicity. Mannitol may accumulate in the brain parenchyma, especially in an injured area, possibly leading to a rebound effect of increasing ICP when it is discontinued. Preventing hypovolemia following mannitol administration may reduce this complication[8,13] (Box 100-3).

100.7.2.5.2

Hypertonic Saline

Hypertonic saline is a useful therapy for ICH.[8,10,14,15] Animal models have shown it to be as effective as mannitol in reducing cerebral water content.[14] It may also have beneficial effects on excitatory neurotransmitters, as well as on the immune system.

Recommended dosage is sodium chloride 7.5% solution 4 ml/kg IV over 5 to 10 minutes.

100.7.2.5.3

Furosemide

In animals in which mannitol fails to control ICP, or if mannitol is not indicated because of cardiac or electrolyte abnormalities, or ongoing intracranial hemorrhage is suspected, furosemide may be given. Furosemide is a loop diuretic that may reduce brain water by promoting a diuresis of hypoosmotic urine, in addition to other undetermined ICP-lowering effects. Administration of furosemide simultaneously with mannitol reportedly has been synergistic in reducing ICP.[4]

Recommended dosage of furosemide is 0.7 to 2 mg/kg IV. Furosemide takes effect within 30 minutes following IV administration. Maintenance of fluid and electrolyte balance is required.

100.7.2.5.4

Glucocorticoids

A beneficial role for glucocorticoids in the treatment of head trauma remains unproven, and their routine use is strongly discouraged by these authors.[11] Until such time as appropriate studies support the use of glucocorticoids in the treatment of ICH caused by traumatic brain injury, their use is not recommended.[11] Primary infectious and non infectious inflammatory diseases and tumor-associated edema may be indications for considering glucocorticoids to treat severe ICH.[16]

100.7.2.5.4.1

Box 100-3 Precautions for Use of Mannitol

1. Maintain euvolemia. Correct hypovolemia before use, but do not overhydrate. A catheter placed in the urinary bladder to monitor urine output facilitates this aspect of treatment.
2. Use a fluid line filter when administering mannitol or dissolve visible crystals in solution before use.
3. Administer as a slow bolus over 20 minutes.
4. If possible, monitor and maintain serum osmolality at or below 320 mOsm/L, particularly when there is concern for renal failure.
5. Monitor serum electrolytes and acid base balance and maintain in normal range.
6. Monitor urine output. If urine is not produced within 15 minutes of mannitol administration, give furosemide to induce diuresis.

7 Do not use when clear evidence of ongoing intracranial hemorrhage is present, for example, imaging evidence.

Recommended dosage is dexamethasone sodium phosphate 0.1 to 0.25 mg/kg IV.

100.7.2.5.5 Other Drugs

While the authors do not recommend usage of additional drugs for the treatment of ICH, several drugs have been recommended. Dimethyl sulfoxide (DMSO) and opioid antagonists (e.g., naloxone) have been used to treat brain edema, although there is no evidence to support their use in place of mannitol. Tirilazad mesylate has shown promise as a neuroprotectant in experimental models of focal cerebral ischemia and subarachnoid hemorrhage. Research is ongoing concerning use of agents such as tromethamine (an alkalinizing agent), superoxide dismutase, allopurinol, thyrotropin-releasing hormone, fluosol, and calcium channel blocking drugs.[13]

100.7.2.6 Cerebral Metabolic Rate of Oxygen Consumption

CBF and cerebral metabolic rate (CMR) are coupled so that an increase CMR is accompanied by a rise in CBF. Reducing the oxygen requirement of the brain may reduce ICP by reducing cerebral blood volume. Hyperthermia, fever, and hallucinogenic drugs (e.g., ketamine) increase the oxygen requirements of the brain. Measures to reduce CMR include sedation with barbiturates, anesthesia, and hypothermia.[10,11]

100.7.2.7 Surgical Therapy

Craniectomy should be considered in animals with ICH refractory to medical decompression. Other indications for surgery include debulking of mass lesions, drainage of intracranial abscesses, and treatment of open skull fractures, depressed skull fractures, or fractures involving a venous sinus or middle meningeal artery.[1,13] Durotomy appears to be significantly more effective than skull removal in lowering ICP experimentally in dogs and cats.[13]

In humans, aspiration of CSF via intraventricular catheterization is used frequently to treat ICH.[10] It may be possible to aspirate CSF from animals with ventriculomegaly, and ultrasound-guided CSF aspiration may be considered in animals with fontanelles.

100.7.2.8 Other Considerations

Intensive supportive care, as discussed in various sections of this manual, is essential. Factors such as frequent turning, prevention of pressure sores, nutritional support, and attention to bladder and bowel function are of paramount importance in preventing complications associated with recumbency. Most animals with ICH have depressed swallowing and gag reflexes, so oral feeding should be avoided, because aspiration pneumonia may result. Alternative methods of nutritional support, such as a feeding tube or total parenteral nutrition, should be considered early in the course of treatment.

100.8 PROGNOSIS

In general, animals with brain stem lesions, especially persistent coma, abnormal respiration, or progressive loss of cranial nerve reflex function, have a poorer prognosis than those with cerebrocortical involvement. Patience and persistence are essential in treatment, because recovery may require a prolonged time for resolution of edema, necrosis, and hemorrhage. Also, compensatory mechanisms of the central nervous system often require many months for maximum development. Even animals with residual deficits may be functional pets. 428 429

100.9 SUGGESTED FURTHER READING*

RS Bagley: Pathophysiology of nervous system disease. In RS Bagley (Ed.): *Fundamentals of veterinary clinical neurology*. ed 1, 2005, Blackwell, Oxford, *A chapter that provides a logical, easy-to-read overview of intracranial physiology, with specific detail relating to dogs and cats*.

RS Bagley: Treatment of important and common diseases involving the intracranial nervous system of dogs and cats. In RS Bagley (Ed.): *Fundamentals of veterinary clinical neurology*. ed 1, 2005, Blackwell, Oxford, *A concise and relatively complete summary of treatment modalities recommended for animals with ICH, and specific recommendation for various intracranial diseases*.

AM Marmarou, A Beaumont: Physiology of the cerebrospinal fluid and intracranial pressure. In HR Winn (Ed.): *Youmans neurological surgery*. ed 5, 2004, Saunders, Oxford, *The human neurosurgeon's "bible" on general intracranial physiology*.

J Proulx, N Dhupa: Severe brain injury. Part I. Pathophysiology. *Comp Cont Educ Pract Vet*. **20**, 1998, 897, *The first article in a two-part series reviewing human and veterinary concepts in the pathophysiology of traumatic brain injury*.

J Proulx, N Dhupa: Severe brain injury. Part II. Therapy. *Comp Cont Educ Pract Vet*. **20**, 1998, 993, *The second article in a two-part series reviewing management modalities for traumatic brain injuries in animals*.

* See the CD-ROM for a complete list of references

101 Chapter 101 Lower Motor Neuron Disease

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101.1 KEY POINTS

- The motor unit is comprised of the lower motor neuron (LMN), the neuromuscular junction (NMJ), and skeletal muscle fibers.
- Disease of the motor unit results in flaccidity, diminished segmental reflexes, and rapidly progressing muscle atrophy.
- In contrast, upper motor neuron (UMN) paresis or paralysis results in spasticity and exaggerated segmental reflexes.
- Clinical signs, clinicopathologic testing, and electrodiagnostic testing can be used to identify the location of the disease within the motor unit.
- Cranial or spinal neuropathies and local or diffuse myopathies result from neoplastic, degenerative, genetic, immune-mediated, metabolic, vascular, toxic, infectious, or idiopathic causes. Botulism, tick paralysis, acquired myasthenia gravis, or aminoglycoside intoxication may cause diffuse junctionopathies.

101.2 INTRODUCTION

The lower motor neuron (LMN) is comprised of the cell body (found in the brainstem or spinal cord) and the axon that contributes to either the spinal or cranial nerves. The LMN terminates on skeletal muscle fibers at the neuromuscular junction (NMJ). The LMN, NMJ, and skeletal muscle fibers together make up the motor unit.[1]

The upper motor neuron (UMN) system originates in the cerebral cortex and brainstem, with axons contributing to the corticospinal, rubrospinal, reticulospinal, or vestibulospinal tracts. The UMN is confined to the central nervous system and terminates on the LMN. Strictly defined, the UMN is a *premotor* neuron because it results only in movement and muscle tone through its actions on the LMN.[2]

The paretic or paralyzed patient may have disease of the brain, spinal cord, nerve, NMJ, or skeletal muscle. The neurologic examination and its interpretation are the first and most important steps in localizing the lesion. The first question asked is whether the clinical signs result from dysfunction of the UMN system or of the motor unit. Disorders of the UMN system typically result in spasticity and exaggerated segmental reflexes. Disorders of the motor unit result in flaccidity, diminished segmental reflexes, and rapidly progressing muscle atrophy (over 1 to 2 weeks). This chapter will describe how to recognize diseases of the motor nerve (neuropathy), NMJ (junctionopathy), and muscle (myopathy), how to confirm an anatomic diagnosis, and how to treat specific disorders of the motor unit.

101.3 IDENTIFYING NEUROPATHIES, JUNCTIONOPATHIES, AND MYOPATHIES

Disease of the motor unit results in flaccid paresis or paralysis. A short-strided gait is apparent when appendicular muscles are involved. Postural reactions and segmental reflexes frequently are diminished. Muscle atrophy is common, although involvement of specific muscle groups may result in specific dysfunction including incontinence, dysphagia, dysphonia, regurgitation, and abnormal facial expressions. In order to generate a list of appropriate differential diagnoses, the location of the lesion (nerve, NMJ, muscle) must first be determined using information from the clinical examination, clinicopathologic tests, electrodiagnostic testing, and/or biopsy.

101.3.1 Clinical Signs

Some clinical signs are specific to involvement of the nerve, NMJ, or skeletal muscle. Because neuropathies may affect sensory neurons in addition to the LMN, proprioceptive deficits and diminished tactile or pain sensation may be recognized with neuropathies, but not with diseases of the NMJ or muscle. In some instances, it can be difficult to distinguish whether an animal does not correct a knuckled over paw due to inability to sense that it is in an abnormal position (diminished proprioception) or due to paresis. If one supports most of the animal's weight and places the dorsal surface of the paw on the floor, a paretic dog may replace the foot promptly, but a dog with significant proprioceptive deficits will not. Additional clinical signs that may suggest the location of the lesion are muscle pain (found with some myopathies) and waxing and waning signs that frequently are made worse with exercise (found with some junctionopathies and myopathies but uncommon with neuropathies).

101.3.2 Clinicopathologic Testing

Serum enzyme activities specific to muscle may help to identify myopathic disease. Large increases in the serum concentrations of the enzymes creatine kinase, serum glutamic aspartate aminotransferase, and lactate dehydrogenase can indicate damage to muscle fibers. Increases in serum activities of these enzymes must be interpreted with caution because damage to muscle may also occur from recumbency and trauma associated with any cause of paresis.

Cerebrospinal fluid (CSF) analysis may be useful to identify neuropathic disease. Many neuropathies, particularly those involving the nerve roots (radiculopathies) due to degenerative, neoplastic, or inflammatory processes can result in elevations in CSF protein and pleocytosis. These elevations are not expected in most myopathies or junctionopathies.

101.3.3 Electrodiagnostic Testing

Electrodiagnostic testing that is useful for evaluating disease of the motor unit includes electromyography (EMG) and evoked response testing. Electromyography can detect electrical discharges of muscle fibers that are independent of neural control. Spontaneous electrical activity known as *fibrillation potentials* and *positive sharp* commonly are recorded from damaged (myopathy) or denervated muscle (neuropathy) but are rarely found in junctionopathies.

Nerve fibers may also be stimulated electrically to produce compound muscle action potentials (CMAPs). The amplitude and duration of these evoked potentials and the conduction velocity along the nerve can be used to identify the location of the lesion. Small-amplitude evoked responses are found in neuropathies where axonal dysfunction is present (axonal neuropathies), and they can also be found with some junctionopathies and myopathies. Repetitive nerve stimulation is useful for identifying junctionopathies because it often causes the evoked CMAPs to have decreasing amplitude in cases of myasthenia gravis and increasing amplitude in animals with tick paralysis and botulism. A prolonged duration of the CMAP and a significant decrease in nerve conduction velocity can occur in neuropathies where myelin dysfunction occurs (demyelination neuropathies).

101.3.4 Nerve and Muscle Biopsy

Nerve and muscle biopsies may be required when electrodiagnostic testing cannot be performed or when the results of these tests are inconclusive. Nerve biopsy may reveal degeneration or inflammation of the axon or myelin associated with the neuropathy. Muscle biopsy may reveal fiber-type grouping, group atrophy, degeneration, inflammation, or infiltration with fat and connective tissue. Fiber-type grouping, the clustering of either type I or type II muscle fibers, and group atrophy (atrophy of adjacent muscle fibers of similar type) can be seen in animals with neuropathies. Myopathies generally are characterized by fibers affected in a more random pattern with muscle necrosis, regeneration, and inflammation commonly found.[2]

101.4 DECISION MAKING

When an animal has signs consistent with disease of the motor unit, the clinician should first determine which nerve and muscle are affected, based on the clinical examination. If a neuropathy is suspected, the distribution of the neuropathy should be ascertained (cranial versus spinal nerves, mononeuropathy versus polyneuropathy, purely motor neuropathy versus concomitant sensory or autonomic neuropathy).[3] The distribution should be determined in a similar fashion in animals with myopathies (localized versus generalized). A list of differential diagnoses can then be generated.

Next, the onset and course of the clinical signs should be considered. Acute disease may be due to metabolic, neoplastic, inflammatory, traumatic, toxic, and vascular causes, with bilaterally symmetric disease resulting more commonly from metabolic, inflammatory, and toxic causes and asymmetric disease resulting more commonly from neoplastic and traumatic causes.

Next, the possible association of the neurologic dysfunction with any past or present diseases should be considered. Hematologic, biochemical, and serologic testing, as well as imaging, may be performed.

Finally, electrodiagnostic testing, nerve biopsy, and muscle biopsy may be done to confirm the distribution of the disease and to determine the nature of the lesion.

101.5 CAUSES OF ACUTE NEUROPATHY, MYOPATHY, OR JUNCTIONOPATHY

101.5.1 Cranial Mononeuropathies

101.5.1.1 Trigeminal Nerve Sheath Tumor

The client frequently recognizes a rapid loss of muscle over one side of the head of the dog, even though the malignant peripheral nerve sheath tumor (MPNST) is slow growing. Unilateral temporal, masseter, pterygoid, and digastric muscle atrophy may occur, the mandible may be directed toward the side of the lesion, and a unilateral loss of facial sensation may occur if sensory fibers are involved. As the mass grows and compresses the brain, signs of brainstem dysfunction may occur with hemiparesis and vestibular system dysfunction being particularly common. Diagnosis generally is made by computed tomography (CT) or magnetic resonance imaging (MRI) of the head. Surgery and radiation therapy have been attempted and may slow the progression of signs.[4]

101.5.1.2 Trigeminal Neuritis

Dogs (common) and cats (rare) with trigeminal neuritis have an acute inability to close the mouth and difficulty eating and drinking due to bilateral paralysis of the mandibular muscles. Decreased sensation of the face, due to involvement of sensory nerve fibers, and Horner syndrome, due to presumed involvement of sympathetic fibers adjacent to the ophthalmic branch of the trigeminal nerve, may also occur. The diagnosis is made by ruling out musculoskeletal causes for a dropped jaw. Other differential diagnoses for mandibular paralysis are rabies encephalitis (the clinician should wear gloves and obtain a complete vaccination history), round cell neoplasia, and early polyneuritis.[5] Treatment is supportive and the animal is fed by placing small meatball-shaped foods in the mouth with the head elevated. Recovery usually occurs in 2 to 4 weeks, although up to 9 weeks is described.

101.5.1.3 Facial Nerve Paralysis

Dogs and cats generally present because of an inability to lift the lip, excessive drooling, and an inability to move the ear or blink the eyelid. Unilateral (common) or bilateral (less common) paralysis may occur. Signs may be due to inflammatory, neoplastic, traumatic, and idiopathic causes.[6] In the idiopathic form, which may be the most common, tear production is preserved and signs may resolve in weeks to months with no specific therapy. Facial nerve paralysis due to otitis media/interna is indistinguishable from the idiopathic form unless accompanied by Horner syndrome or evidence of ear disease identified by otic examination, brainstem auditory evoked response testing, or imaging.

Surgical (bulla osteotomy) or medical therapy (cephalosporins, amoxicillin-clavulanic acid, clindamycin, enrofloxacin) of the ear disease may lead to resolution of the paralysis. Trauma to the nerve may occur following total ear canal ablation and may or may not resolve with time. Lymphosarcoma may also cause unilateral facial nerve paralysis. In these cases, the facial nerve typically is affected intracranially, in which case the major petrosal nerve may also be affected, resulting in decreased tear production.[7] Finally, facial nerve paralysis may be a clinical sign of a polyneuropathy.

101.5.1.4 Laryngeal Paralysis

Dogs and cats with increased inspiratory sounds, dysphonia, gagging, cyanosis, panting, and collapse may have disease of the vagus or recurrent laryngeal nerves. Laryngeal paralysis may be unilateral or bilateral and may be due to trauma, degeneration (hypothyroid, polyneuropathy), toxic (lead, organophosphates) or idiopathic causes, and has a genetic basis in Siberian Huskies, Bouvier des Flandres, Dalmatians, Rottweilers, Bull Terriers, German Shepherds, and Pyrenean Mountain Dogs (IVIS).[8,9]

The diagnosis is made under light sedation, preferably using thiopental, where decreased abduction of vocal folds with inspiration is found. Electromyography may reveal spontaneous electrical activity in the cricoarytenoideus dorsalis muscle, and in many cases evidence of a distal appendicular polyneuropathy that may or may not be clinically apparent is found. Treatment consists of exercise restriction, tranquilization, and cooling the patient. Arytenoid lateralization surgery may eventually be necessary.

101.5.2 Cranial Polyneuropathies

101.5.2.1 Paralysis of Oculomotor, Trochlear, Abducens, and Trigeminal Nerves

Dogs and cats may have unilateral or bilateral internal and external ophthalmoplegia (inability to move the eyes, retract the globe, or move the pupil). Additional signs may include ptosis and diminished sensation to the cornea and the skin around the eye. These signs can occur from tumors or inflammatory disease of the middle cranial fossa involving these nerves where they pass near the cavernous sinus, or from disease of the retrobulbar space.[10] CT or MRI is necessary to further characterize the lesion before therapy is begun.

101.5.2.2 Other Causes of Cranial Polyneuropathy

Animals may occasionally have dysfunction of multiple cranial nerves including the trigeminal, facial, vestibulocochlear, vagus nerves, and others. Signs may be bilaterally asymmetric or symmetric. Progression of signs from a mononeuropathy to a polyneuropathy may occur. In these animals, tumors and inflammation of the brain stem and cranial nerves must be considered. Lymphosarcoma and meningiomas commonly affect several adjacent cranial nerves, and diagnosis is made with CT and MRI of the brain and cranial nerves, in addition to biopsy. Fungal and protozoal meningoencephalitides may also affect several cranial nerves with diagnoses made by CSF analysis or titers in CSF or serum. Rabies encephalitis must also be considered as a cause of acute-onset cranial polyneuropathy.

101.5.3 Spinal Mononeuropathies

Spinal mononeuropathies and multiple mononeuropathies generally are due to trauma (transections, stretching, bite wounds, injections) and may be classified into three categories based on lesion severity. Neurapraxia, the loss of nerve conduction without structural change, occurs from transient loss of blood supply, often due to compression, and usually resolves over weeks to months. Axonotmesis, damage to axons without loss of supporting structures, requires regeneration of the axons in a favorable environment where motion is absent. Regeneration progresses at a rate of approximately 1 mm per day. Neurotmesis is complete severance of the nerve. Clinical signs seen with disease of specific nerves are well described and the lesion severity may be determined by visual inspection, repeated clinical examinations, and electrodiagnostic testing.[1,7,11] Sharp transections may respond well to surgical intervention, but effective therapy for traction injuries has not been described.

Malignant peripheral nerve sheath tumors and round cell tumors may also result in spinal mononeuropathies, multiple mononeuropathies, and polyneuropathies. They are discussed in the section below.

101.5.4 Spinal Polyneuropathies

101.5.4.1 Metabolic Causes

Metabolic causes of neuropathy generally have an insidious onset. Hypoadrenocorticism and diabetes mellitus may cause rear limb paresis in addition to signs of metabolic disease. Dogs with Addison disease may manifest signs ranging from rear limb paresis to recumbency. Diabetic animals may have a plantigrade stance.

In both instances hyporeflexia may occur. Hypothyroid neuropathy is also described with generalized weakness, muscle atrophy, and hyporeflexia with or without diminished facial sensation, facial nerve paresis, laryngeal paralysis, megaesophagus, vestibular system dysfunction, and lameness.[12] Control of metabolic disease commonly results in resolution of neurologic dysfunction.

Serum glucose concentrations of less than 50 mg/dl due to insulin-secreting tumors may result in flaccid paresis or paralysis, hyporeflexia, lethargy, bradycardia, muscle tremors, hypothermia, and disorientation, with or without seizures. Small quantities of food high in protein, fat, and complex carbohydrates may be provided frequently. Diazoxide (10 mg/kg q12h) and prednisone (0.5 to 1.0 mg/kg q24h) may be given, and surgical tumor resection is often beneficial.

101.5.4.2 Malignant Peripheral Nerve Sheath Tumors and Round Cell Tumors

MPNSTs and round cell tumors are the most common tumors to involve peripheral nerves. Both tend to affect proximal motor nerves (near the spinal cord), but although MPNSTs affect adjacent nerves on one side of the spinal cord, round cell tumors may cause bilateral paresis or paralysis. MPNSTs more commonly affect spinal nerves to the thoracic limbs rather than those to the pelvic limbs. Both tumors are sometimes palpable and painful and can be diagnosed with MRI or CT and biopsy. MPNSTs are treated with radical resection of the nerves because a nonresected tumor has a tendency to regrow into and compress the spinal cord.[13] Round cell tumors are treated with radiation or chemotherapy.

101.5.4.3 Toxoplasmosis and Neosporosis

Puppies may manifest flaccid paralysis of the pelvic limbs that progresses to increased extensor tone of such a degree that the joints no longer bend. Signs of neuropathy and myopathy may occur, and retinitis may accompany these signs. Diagnosis is made by finding protozoa on muscle or nerve biopsy or by finding increased serum antibody titers. Trimethoprim-sulfadiazine (15 mg/kg PO or IV q12h for 2 weeks) and clindamycin (10 mg/kg PO or IV q12h for 8 weeks) may result in improvement of clinical signs; however, once hind limb rigidity has developed, improvement will not occur with therapy.[14]

101.5.4.4 Acute Polyneuritis and Polyradiculoneuritis

Affected dogs may have a history of exposure to raccoons, recent vaccination, or neither. Flaccid tetraparesis or paralysis and hyporeflexia develop within 1 to 3 days of the onset of signs. Facial muscle paresis and a change in bark are common. Respiratory paralysis may occur. Tail and neck motion, swallowing, and fecal and urinary continence are often maintained. The animal may be hyperaesthetic to touch. CSF analysis may show an increase in protein, and electromyography may show diffuse fibrillation potentials and positive sharp waves; nerve conduction velocity is slow, and CMAPs may be decreased in amplitude.[15] Biopsy of the nerve or nerve root may show inflammatory cell infiltrates, demyelination, and axonal loss. Titers for *Toxoplasma* and *Neospora* are recommended to rule out these causes of polyneuritis.[16]

Prednisone (1 mg/kg prednisone q12h for 1 to 2 weeks; then 1 mg/kg q24h for 1 month) may be given; however, there is controversy as to whether it has any effect on the progression of this disease. Aggressive supportive care is necessary to prevent and treat decubital ulcers and urinary tract infections. Close observation for respiratory muscle paresis is important. Partial or complete recovery may take 2 to 30 weeks and signs can recur.

101.5.4.5 Aortic Thromboembolism

Animals may have an inability to stand on the pelvic limbs or may have a short-strided, crouched gait with the animal sitting after only a few steps. Peripheral nerves are ischemic and anesthesia may accompany the paresis or paralysis. Limbs are painful and cool, pulses are weak or absent, and muscles are often firm. Abdominal ultrasonography may identify a thrombus in the aorta. Analgesics, intravenous fluids, heparin, vasodilators, and aspirin may be beneficial (see Chapters 117 and 188, Hypercoagulable States and Thrombolytic Agents, respectively). Thromboembolism has been associated with cardiomyopathy in cats and with protein-losing nephropathy in dogs.[17,18]

101.5.4.6 Intoxications

Drugs that may result in neuropathies include vincristine, thallium, and organophosphates. Animals usually manifest an insidious onset of clinical signs and history of drug administration or ingestion.

101.5.5 Localized Myopathies

101.5.5.1 Masticatory Myositis

Animals may have swelling over the head (acute), atrophy of the masticatory muscles (chronic), and trismus. Affected muscles of mastication (temporalis, masseter, pterygoid) may be painful on palpation and the mouth may be difficult to open. Masticatory myositis may be confirmed by muscle biopsy or serum titers for antibodies against type IIM muscle fibers. Treatment with prednisone (1 to 2 mg/kg q12h for 4 weeks and then tapering dosage over several months) results in a resolution of pain and improves mastication. Residual signs of disease including decreased range of motion of the jaw and significant atrophy are common.

101.5.5.2 Megaesophagus

Animals with megaesophagus can present with regurgitation, excessive salivation, and/or aspiration pneumonia (see Chapter 131, Vomiting and Regurgitation). Megaesophagus may occur with neuropathies (lead or organophosphate intoxication, dysautonomia), polymyopathies, and junctionopathies (myasthenia gravis, botulism), although clinical signs of disease elsewhere in the body commonly are found. Idiopathic megaesophagus may be congenital or acquired, and although disease of the vagus nerve is suspected, this has not been confirmed. A diagnosis of idiopathic megaesophagus is made by clinical and radiographic findings and by ruling out obstructive causes, toxic or infectious causes, endocrine disease, and myasthenia gravis. Small, frequent meals offered to an animal with the head and thorax elevated may help food reach the stomach. The smooth muscle prokinetic agents metoclopramide and cisapride have not been helpful in improving esophageal motility in dogs (likely due to the canine esophagus being primarily striated muscle). Reported use in the cat is lacking. Aspiration pneumonia is frequently recurrent and requires long-term management.

101.5.6 Diffuse Myopathies

Dogs and cats of any age may develop polymyositis, which is characterized by generalized weakness that worsens with exercise.[19] The gait is stiff and short-strided. Ventroflexion of the neck, dysphagia, regurgitation, megaesophagus, change in bark, painful appendicular muscles, fever, lethargy, and increases in creatine kinase, serum glutamic aspartate aminotransferase, lactate dehydrogenase, and antinuclear antibody may occur. Electromyography shows fibrillation potentials, positive sharp waves, and complex repetitive discharges in many muscles, and muscle biopsy shows lymphoplasmacytic inflammation and muscle necrosis. Toxoplasmosis and neosporosis should be ruled out with titers and muscle biopsy. 432 433

Prednisone may be given (1 mg/kg q12h initially) and reduced to the lowest dosage necessary to control signs. Pharyngeal and esophageal muscle involvement may result in aspiration pneumonia.

101.5.7 Junctionopathies

101.5.7.1 Botulism

Signs occur in dogs hours to days following ingestion of a toxin produced by *Clostridium botulinum*. The toxin interferes with the release of acetylcholine at the NMJ. A stiff and short-strided gait with muscle tremors (frequently first affecting the pelvic limbs) rapidly progresses to flaccid tetraplegia with diminished to absent spinal reflexes. A decreased ability to blink the eyelids, close the mouth, lift the upper lip, lap water with the tongue, or swallow occurs. Change in bark, mydriasis, regurgitation associated with megaesophagus, constipation, urinary retention, and respiratory paresis or paralysis may occur.

Diagnosis is made by identifying a history of exposure to spoiled meat and by finding other similarly affected animals. Toxin may be identified in food, serum, stomach contents, or feces early in the course of the disease. Supporting the patient may result in complete resolution of signs within 2 to 3 weeks. The patient should be monitored for aspiration pneumonia. A gastrostomy tube or parenteral nutrition may be necessary to provide nutritional support. If acute exposure occurs and signs are progressing, type C antitoxin may be administered.[20]

101.5.7.2 Tick Paralysis

Dogs may have a recent history of ataxia or paresis that may progress to recumbency within 24 to 72 hours. Signs are similar to those found with botulism, but spontaneous nystagmus may be seen and urinary and fecal continence frequently are maintained. A slow nerve conduction velocity may be found in addition to a decreased CMAP amplitude. Signs are due to an unidentified toxin believed to be present in tick saliva that interferes with the release of acetylcholine at the NMJ. In all dogs that develop a sudden onset of flaccid quadriparesis, a thorough examination for ticks should be performed that may include clipping of all hair, bathing the dog, and applying a topical tick treatment. Resolution of clinical signs occurs within 24 to 72 hours of tick removal.[21] Tick paralysis in Australia causes a more severe and prolonged course of disease.

101.5.7.3 Acquired Myasthenia Gravis

Acquired myasthenia gravis has been reported in cats and many breeds of dogs over 8 months of age, with the German Shepherd, Labrador Retriever, and Akita overrepresented. At least three clinical pictures may occur: (1) focal myasthenia gravis, (2) generalized myasthenia gravis, and (3) acute fulminating myasthenia gravis.[22]

Animals with the focal form show facial (decreased palpebral blink with normal sensation), pharyngeal (decreased gag reflex), or laryngeal (voice change, decreased arytenoid and vocal fold abduction, inspiratory stridor) dysfunction without appendicular muscle involvement. Megaesophagus may occur with or without aspiration pneumonia, and the animal may regurgitate within hours after eating. Frequently excessive salivation, dysphagia, change in bark, coughing, and retching are noted.

Generalized myasthenia gravis is characterized by appendicular muscle weakness, with or without signs of facial, pharyngeal, or laryngeal dysfunction. Strength may return following periods of rest, or the animal may show continuous weakness with the rear limbs often more severely affected. The animal has a stiff, short-strided gait, muscle tremors, and may walk “on the toes” of the rear limb. The head and neck may be held low and the dog may pant excessively. Postural reactions are usually normal if the animal is supported. Spinal reflexes and sensation are normal.

Acute, fulminating myasthenia gravis is the most severe form of the disease.[22,23] Signs include a sudden, rapid progression of severe appendicular muscle weakness, resulting in recumbency that is unabated by rest, frequent regurgitation associated with megaesophagus, and facial, pharyngeal, or laryngeal dysfunction. Respiratory dysfunction, thought to be due to aspiration pneumonia and loss of respiratory muscle strength, may be severe.

Definitive diagnosis of acquired myasthenia gravis may be made by identifying increased circulating acetylcholine receptor antibody in blood (>0.6 nm/L in dogs; >0.3 nm/L in cats). Antibodies are detectable in 80% to 90% of dogs with acquired disease. Intercostal muscle biopsy may also be used to identify acetylcholine receptor antibodies at the NMJ. If a more immediate diagnosis is necessary, edrophonium response testing may be performed.

Edrophonium (0.1 to 0.2 mg/kg IV) results in dramatic improvement in gait for 1 to 2 minutes in some animals with myasthenia gravis (anecdotal evidence suggests that improvement is rarely seen in cases of acute fulminating myasthenia gravis). Pretreatment with atropine (0.02 mg/kg IV) is recommended to decrease salivation, defection, urination, bronchial secretion, and bronchoconstriction that may occur following edrophonium administration. The animal may require oxygen and endotracheal intubation if severe dyspnea develops. Electrodiagnostic testing may also be performed. A 10% or greater decremental response of the fourth or fifth compound action potential recorded from the interosseous muscle following repetitive stimulation of the tibial or ulnar nerve at 3 Hz may be found.

Animals affected with generalized myasthenia gravis may be treated with oral pyridostigmine bromide (0.2 to 2 mg/kg q8-12h; IV infusions of 0.01 to 0.03 mg/kg/hr have also been used). Intramuscular neostigmine bromide or methylsulfate (0.04 mg/kg q6-8h) may be given to animals with significant dysphagia and regurgitation. A low dosage is begun and titrated upward over 2 to 3 days until clinical signs resolve or signs of overdose occur (bradycardia, diarrhea, salivation, dyspnea, miosis, and recurrence of weakness). When these signs occur, the dosage is decreased until they are no longer present. The animals should be kept warm and exercise limited. Although appendicular muscle weakness frequently resolves with this care, pharyngeal, laryngeal, and esophageal dysfunction may continue for weeks. 433

434 In animals with focal and generalized myasthenia gravis in whom dysphagia and megaesophagus are marked, pyridostigmine or neostigmine is given; however, management of these patients must include feeding the animal from a raised height and keeping the head elevated for 10 minutes afterward to facilitate passage of food into the stomach. Frequently a gastrostomy tube is necessary to provide nutritional support until dysphagia and regurgitation resolve. Frequent auscultation and radiographs of the thorax are recommended to determine whether aspiration pneumonia is present. If so, a transtracheal wash is performed and broad-spectrum antibiotics are given (see Chapter 23, Aspiration Pneumonitis and Pneumonia). Aminoglycoside antibiotics should be avoided (see Aminoglycoside Intoxication later in this chapter).

Treatment of acquired myasthenia gravis with prednisone is controversial because it may result in a rapid worsening of clinical signs in affected humans. In addition, the immunosuppressive effects of steroid therapy may lead to rapid respiratory deterioration in patients with aspiration pneumonia. Anecdotally, the addition of prednisone to neostigmine improves pharyngeal dysfunction sooner than cholinesterase inhibitors alone. A starting dosage of 0.5 mg/kg/day increased to 2 mg/kg q24h over 1 week has been suggested. Prednisone should be started only in the hospital, where the animal can be monitored for sudden deterioration and for aspiration pneumonia. Additionally, treatment with azathioprine (2 mg/kg PO q12-24h, decrease dosage after 3 to 6 months) and mycophenolate mofetil (10 to 20 mg/kg PO or IV q12h) has proven useful and may minimize side effects of steroid administration.[24,25]

The acquired disease is usually a temporary state and may resolve over many months of supportive care. The most common cause of death or euthanasia is aspiration and pneumonia. In nine cases of acute, fulminating myasthenia gravis reported in the literature, eight died or were euthanized because of respiratory failure and aspiration despite anticholinesterase inhibitor therapy in some cases.[22,23] Plasmapheresis and intravenous γ-globulins may, in the future, prove useful in treating acute, fulminating disease.

In approximately 15% of dogs with acquired myasthenia gravis, the disease is related to a thymoma. In these cases, thymectomy may resolve clinical signs. Other inciting causes include osteogenic sarcoma, biliary carcinoma, and reaction to exogenous antigens. One paper describes an association between hypothyroidism and myasthenia gravis in dogs and suggests that testing for hypothyroidism be performed in cases of the latter. Thyroid supplementation should be instituted if necessary.[26]

101.5.7.4 Aminoglycoside Intoxication

Animals may have a history of recent parenteral aminoglycoside exposure. Affected animals are tetraparetic and clinical signs generally resolve following discontinuation of aminoglycosides. It is important to note that clinical signs due to many of the diseases listed in this chapter may worsen following therapy with aminoglycosides.

101.6 SUGGESTED FURTHER READING*

KG Braund: *Braund's clinical neurology in small animals: Localization, diagnosis and treatment, online publication, 2005, International Veterinary Information Service* http://www.ivis.org, 2006, Accessed March 21 *An online text that is updated continually to provide information on newly described neurologic disorders.*

A De Lahunta: In *Veterinary neuroanatomy and clinical neurology*. ed 2, 1983, Saunders, Philadelphia, *The most complete text available on both veterinary neuroanatomy and neurology. A thoughtful and complex read suitable for those with a strong interest in veterinary neurology*.

J Evans, D Levesque, GD Shelton: Canine inflammatory myopathies: a clinicopathologic review of 200 cases. *J Vet Intern Med*. **18**, 2004, 679, *A comprehensive retrospective study on 200 affected dogs examining signalment, clinical signs, clinicopathologic findings, electrophysiologic findings, and histopathology used to differentiate various focal and generalized inflammatory myopathies*.

AS Kapatkin, CH Vite: Neurosurgical emergencies. *Vet Clin North Am Small Anim Pract*. **30**, 2000, 627, *A brief review that describes cranial, spinal, and peripheral nerve disease and their therapy in small animals*.

* See the CD-ROM for a complete list of references

102 Chapter 102 Tetanus

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102.1 KEY POINTS

- Tetanus is the result of a bacterial infection by *Clostridium tetani* following a skin wound, surgery, or even parturition.
- The clinical signs are due to the effects of an exotoxin produced by the bacillus that prevents neurotransmitter release.
- Common signs include spasms of the masticatory, pharyngeal, and facial muscles, but the whole body can be involved.
- Definitive diagnosis is difficult in many cases unless serum antibodies can be associated with the bacterial toxin.
- Treatment is initiated immediately on suspicion of the disease based on clinical signs.
- Tetanus antitoxin can prevent further deterioration of the patient from unbound toxin at time of treatment, but improvement relies on regrowth of axons and nerve terminals.
- Broad-spectrum anaerobic antibiotics, wound cleansing, muscle relaxants, and sedatives are the important constituents of medical management.
- A quiet environment and intensive nursing care are essential for the success of treatment regimens.

102.2 ETIOLOGY

Tetanus is caused by the neurotoxins released by *Clostridium tetani,* a motile, gram-positive, nonencapsulated, anaerobic, spore-forming bacterium. The toxin is produced during vegetative growth of the organism in a suitable environment.[1] The deoxyribonucleic acid for this toxin is contained in a plasmid and is antigenically homogenous. The organism's resistant spores are ubiquitous, with a natural habitat in moist fertile soil; however, they can survive indefinitely in dusty indoor environments. Resistance of the spores has been proven to boiling water and an autoclave temperature of 120°C for up to 20 minutes.[2] However, the vegetative phase of this bacterium is susceptible to chemical and physical inactivation. Organisms can be isolated from the feces of dogs, cats, and humans, but presence of the organism does not indicate infection because not all strains possess the plasmid.[1]

Cats and dogs are considered to be relatively resistant to infection by the bacterium, especially when compared with horses and humans. In part the resistance in these species is due to the inability of the toxin to penetrate and bind to nervous tissue.[2]

102.3 PATHOGENESIS

Tetanus develops when spores are introduced into wounds or penetrating injuries. Most cases develop after skin wounds, but infection can follow parturition or ovariohysterectomy.[3-5]

Under anaerobic conditions found in necrotic or infected tissue, the tetanus bacillus secretes two exotoxins: tetanospasmin and tetanolysin. Tetanolysin is capable of locally damaging otherwise viable tissue surrounding the infection and optimizing the conditions for bacterial multiplication.[1]

Tetanospasmin leads to the clinical syndrome of tetanus. This toxin may constitute more than 5% of the weight of the organism.[1] It is a two-chain polypeptide of 150,000 daltons that is initially inactive, made up of a light and a heavy chain. The light chain acts presynpatically to prevent neurotransmitter release from affected neurons. Tetanospasmin binds to the membranes of the local motor nerve terminals. If toxin load is high, some may enter the bloodstream from where it diffuses to bind to nerve terminals throughout the body, and may even enter the central nervous system (CNS) through an intact blood-brain barrier. The toxin is then internalized and transported intraaxonally and in a retrograde fashion to the cell body at a speed of 75 to 250 mm per day.[1,2] Transport occurs first in motor and later in sensory and autonomic nerves. Further retrograde intraneural transport occurs with toxin spreading to the brain stem in a bilateral fashion, up the spinal cord. This passage includes retrograde transfer across synaptic clefts by a mechanism that is unclear.

It is after internalization in inhibitory neurons that the light chain becomes activated; at this stage the toxin is no longer accessible for neutralization by antitoxin.[6,7] It prevents neurotransmitter release by cleaving and inactivating synaptobrevin, a membrane or “docking” protein necessary for the export of intracellular vesicles containing the neurotransmitter.[8] In addition to disrupting docking proteins, the toxin may lead to cross-linking of synaptic vesicles to the cytoskeleton, further preventing neurotransmitter release.[9]

The toxin predominantly affects inhibitory interneurons, inhibiting release of glycine and γ-aminobutyric acid (GABA).[1,7] Interneurons inhibiting α-motor neurons are first affected, and the motor neurons lose inhibitory control. The disinhibitory effect on the motor neuron may cause diminution of function at the neuromuscular junction, so the clinical effect is dissimilar to that of the related botulinum toxin. Medullary and hypothalamic centers may also be affected. Disinhibited autonomic discharge leads to disturbances in autonomic control, with sympathetic overactivity and excessive plasma catecholamine levels.

Neuronal binding of toxin is thought to be irreversible. Recovery requires the growth of new nerve terminals, which explains the long duration of tetanus.[10]

102.4 CLINICAL PRESENTATION

Clinical signs can take up to 3 weeks from the onset of infection to be apparent, although most cases exhibit

symptoms within 5 to 12 days.[11] The clinical signs initially can be localized or generalized, with the former possibly being more common in dogs and cats. A study of 38 dogs with tetanus revealed that ocular and facial changes were the most common initial signs. Localized signs begin proximal to the site of introduction of the infection and can include single muscle rigidity, entire limb rigidity, and facial muscle spasms. The clinical signs may progress with more extensive muscle involvement.[12] Generalized signs include a stiff gait affecting all limbs, increased muscle tone, dyspnea, an elevated tail and a “sawhorse stance,” although the animal may become uncomfortable standing with such excessive muscle activity. At least 50% of dogs will progress within a median of 4 days (range 0 to 14 days) to recumbency with severe muscle spasms.

Involvement of the head can lead to spasms of the masticatory and pharyngeal muscles, causing trismus (lockjaw) and dysphagia. This can be functionally exacerbated by increased salivation, increased bronchial secretions, and increased respiratory rate resulting from involvement of the parasympathetic and somatic cranial nerve nuclei. Regurgitation and gastroesophageal reflux can result rarely from esophageal hiatal hernia and megaesophagus, which may lead to aspiration pneumonia when combined with the problems described earlier.[13] Excessive contraction of the facial muscles causes erect ears and a wrinkled forehead (Color Plate 102-1), and gives the animal a characteristic sneering of the lips known as *risus sardonicus,* or the *sardonic grin* (Color Plate 102-2).[7] Additionally, the patient can exhibit protrusion of the third eyelid and enophthalmos, resulting from retraction of the globe from hypertonus of the extraocular muscles.[12] Reflex muscle spasms can occur in animals with generalized tetanus or intracranial involvement; these may be painful and resemble seizure activity, affecting agonist and antagonist muscle groups together.[12] Severe progression of signs can cause recumbency, opisthotonus, seizure-like activity, respiratory paralysis, and central respiratory arrest, potentially causing death if not rapidly recognized and managed.[7] Death was reported in 18% of dogs (7 of 38) in one retrospective study, and 6 of these dogs demonstrated concurrent autonomic signs.

It is possible to see an effect on the autonomic system evidenced by episodes of bradycardia and tachycardia, hypertension, marked vasoconstriction, and pyrexia.[12,14,15] A study of 38 dogs with tetanus revealed that 37% demonstrated abnormalities of blood pressure or rectal temperature, or both, consistent with autonomic disturbance. In the mild generalized cases, autonomic involvement may be manifested by dysuria and urinary retention, constipation, and gaseous distention. In humans, “autonomic storms” occur, causing marked cardiovascular instability, severe hypertension alternating with profound hypotension, and even recurrent cardiac arrest.[1] During these “storms,” plasma catecholamine levels are raised up to 10-fold, similar to levels seen in animals with a pheochromocytoma.[1]

A neurologic examination of these patients can reveal normal initiation of a response to postural reaction testing but a stiff and reduced motor response.[2] Myotatic reflexes are generally accentuated and flexor reflexes depressed, but both may be difficult to assess because of the extreme rigidity of the limbs. Although a complete neurologic examination is always ideal, it should be emphasized that animals can become very sensitive to tactile, visual, or auditory stimulation that can exacerbate clinical signs, occasionally causing a mild, generalized form of the disease to progress to a crisis situation.

102.5 DIAGNOSIS

The patient history and clinical signs are usually sufficient to make a presumptive diagnosis of tetanus. If general anesthesia is used for diagnostic tests such as cerebrospinal fluid acquisition, the muscle spasms can be reduced but rarely are abolished. Intubation may be difficult in patients with trismus, and a stylet-assisted intubation should be anticipated in severely affected animals (see Supportive Intensive Care).

A complete blood count may suggest an infectious process from a wound, whereas serum biochemistry (with the exception of muscle enzymes) and cerebrospinal fluid analysis findings are normal.[12] Muscle enzymes may be elevated in patients with tetanus because of the persistent muscle spasticity. Radiographs may be helpful to identify involvement of the esophagus, diaphragm, and secondary changes in the lungs resulting from aspiration pneumonia.

Electrodiagnostic abnormalities of tetanus are nonspecific and consist of prolonged electric discharges following needle insertion on electromyography; nerve conduction velocities are normal.[11]

Measurement of serum antibodies to tetanospasmin can be performed by some laboratories and may be used for a definitive diagnosis.[7] Values need to be compared with those of control animals.

Attempts to isolate *C. tetani* from wounds often fails because of the low concentration of organisms and the requirement for strict anaerobic culture conditions at 37°C for at least 2 weeks.[7] Performing a Gram stain on a smear from an open wound may identify gram-positive rods and dark-staining spheric endospores, but the morphology of the bacterium is similar to that of many other bacteria.[12]

102.6 TREATMENT

Treatment strategies involve three principles: organisms present in the body should be destroyed to prevent further toxin release; toxin present in the body outside of the CNS should be neutralized; and the effects of the toxin already in the CNS should be minimized.

102.6.1 Neutralization of Unbound Toxin

Antitoxin neutralizes any toxin that is unbound to the CNS or is yet to be formed. Therefore the timing of administration in relation to the onset of the disease is essential to its efficacy. The antitoxin used can be either antitetanus equine serum or human tetanus immune globulin. The latter may be more likely to produce reactions if given intravenously.[16] Early intervention has been recommended as a matter of routine, but there are no studies objectively evaluating antitoxin use in dogs or cats, and its efficacy in cases with no evidence of a recent wound is unknown.

The recommended dosage of equine antitoxin for dogs and cats is 100 to 1000 U/kg (maximum 20,000) IV, SC, or IM.[2] Intravenous administration is preferred to intramuscular or subcutaneous administration. However, intravenous use of antitoxin is associated with a high incidence of anaphylaxis.[2] To reduce this risk, a test dose (0.1 to 0.2 ml of 1:10.000 solution) should be administered intradermally 15 to 30 minutes before the intravenous dose.[2] A wheal at the site of injection may indicate that an anaphylactic reaction will develop. Epinephrine (0.1 ml/kg IV of the 1:10,000 dilution), glucocorticoids, and an antihistamine should be readily available in case of an adverse reaction (or even given on a prophylactic basis). Repeated doses of antitoxin are more likely to cause adverse reactions and are not recommended or necessary because therapeutic levels persist for approximately 14 days.

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Intramuscular injection at and proximal to the wound site (1000 U) may be helpful in localized forms of tetanus.[2] Although intrathecal administration of antitoxin has not been proven to be effective,[16] experimental studies have suggested that it may be of use in dogs, reducing both the morbidity and mortality in affected patients.[2] It is considered potentially advantageous, because it need not penetrate the blood-brain barrier when given intrathecally and may partially neutralize bound toxin.[2] However, because of the lack of thorough clinical evaluation and risks associated with administration, the intrathecal route should be reserved for severely affected cases.

102.6.2 Removal of Source of Infection

Any obvious wounds should be radically debrided after the administration of antitoxin. Flushing the wound with hydrogen peroxide increases oxygen tension, which inhibits anaerobic organisms, although wound healing may also be impaired[2] (see Chapter 157, Wound Management).

Antibiotics are essential to kill vegetative *C. tetani* organisms and thereby reduce the amount of circulating toxin. Although local administration of antibiotics at a wound site has been advised, parenteral administration is recommended more routinely.[2] Classically, penicillin G has been the management of choice, either intravenously as an aqueous potassium or sodium salt or intramuscularly as the procaine salt (20,000 to 100,000 U/kg q6-12h for 10 days in both cats and dogs). However, metronidazole (10 mg/kg PO or IV q8h for 10 days) has been shown to be superior to penicillin G in clinical tetanus because it achieves bactericidal therapeutic concentrations in anaerobic tissues.[2] Other options include clindamycin (10 mg/kg PO, IV, or IM q8-12h) and tetracycline (22 mg/kg PO or IV q8h).[2]

102.6.3 Control of Rigidity and Spasms

See Anesthesia and Pain Management section and Chapter 184, Narcotic Agonists and Antagonists, for more details on specific therapies.

Prevention of unnecessary stimulation is mandatory, but the mainstay of treatment is sedation with a benzodiazepine. Benzodiazepines augment GABA agonism at the $GABA_{\alpha}$ receptor. Diazepam (0.5 to 1 mg/kg PO q8h in dogs [maximum 10 mg], 0.25 to 0.5 mg/kg in cats [maximum 5 mg], or a continuous intravenous infusion of 0.1 to 1 mg/kg/hr in dogs and cats) or clorazepate (0.5 to 1 mg/kg PO q8h in dogs; 0.2 to 0.5 mg/kg PO q12-24h in cats) can be used in this regard, although both may cause oversedation in some patients.

Additional sedation can be provided by anticonvulsants, particularly phenobarbital (1 to 4 mg/kg PO or IV q12h or IM q6h), which further enhances GABAergic activity. Phenothiazines appear to be highly effective in controlling the hyperexcitable state; chlorpromazine (0.5 to 2 mg/kg IM, IV, or PO q6-12h) is the drug of choice, although acetylpromazine (0.005 to 0.05 mg/kg IV q2h as needed [maximum 3 mg in any dog]) is a useful substitute.

With severe signs such as generalized tonic-clonic seizure activity, generalized body stiffness, and opisthotonus, barbiturate or propofol infusions may be necessary, but cardiovascular parameters should be monitored closely and careful consideration should be given as to whether the patient should be intubated and placed on positive-pressure ventilation. Sedation with propofol has been shown to assist with muscle spasm and rigidity control in humans, without the use of neuromuscular blocking drugs.[17] Neuromuscular blocking agents may be an option for the most severely affected veterinary patients, but assisted ventilation is imperative.

Narcotics and parasympatholytics such as atropine should be used with caution. In severe human forms of tetanus, atropine infusions have helped to control autonomic dysfunction.[18]

102.6.4 Supportive Intensive Care

Intensive nursing care is essential for successful treatment of patients with tetanus. The dog or cat should be isolated in a dark and quiet environment, with cotton wool balls placed in the external ear canals (Color Plate

102-3). Minimal handling is optimal, and all treatments should therefore be coordinated to occur together at set times through the day. A recent study of 10 dogs with tetanus documented the complications that occurred in these dogs during treatment; these included aspiration pneumonia, upper respiratory tract obstruction requiring tracheostomy, and coxofemoral luxation.[i]

Weight loss and dehydration are common in patients with tetanus resulting from poor prehending, mastication, and swallowing capabilities, reduced gastrointestinal function in the presence of autonomic dysfunction, increased metabolic rate, and hyperthermia from the muscular activity and prolonged critical illness. Nutrition and fluid therapy should therefore be established as early as possible. Enteral nutrition may be associated with a lower incidence of complications and is cheaper than parenteral nutrition, but the latter may be necessary in select cases. The risk of vomiting and subsequent aspiration pneumonia must be considered when making this decision (see Chapters 13 and 14, Enteral Nutrition and Parenteral Nutrition, respectively).

Percutaneous gastrostomy may prevent the complications associated with nasogastric tube feeding, particularly the stress that may be associated with an indwelling intranasal tube. Gastrostomy- or gastrojejunostomy-assisted feeding can also reduce the risk of aspiration pneumonia, a potential complication in dogs with severe forms of tetanus and those that are recumbent for a prolonged period.

If airway constriction due to laryngeal spasms, a buildup of saliva or tracheal secretions, or the need for artificial ventilation are concerns, tracheostomy usually is performed after intubation (see Chapter 18, Tracheostomy). A stylet may be inserted into the airway and the endotracheal tube fed over the stylet for intubation of dogs with severe laryngospasm. A tracheostomy requires meticulous care to prevent introduction of infection, but it will allow intermittent tracheal suction to be performed with little stress to the animal. Oxygen supplementation may be administered via tracheostomy flow-by, intratracheally, or with mechanical ventilation.

Urinary and fecal retention occur in some patients with hypertonic anal and urinary sphincters. An indwelling urinary catheter may be beneficial in these patients, although the urine should be analyzed regularly for evidence of infection.

Pressure sores or decubital ulcers should be prevented with appropriate soft or padded bedding and frequent turning and physiotherapy. However, the balance between frequent physiotherapy and isolated rest is difficult to achieve, and pharmacologic sedation may be necessary before physical manipulation is possible in some patients.

102.7 PROGNOSIS

Most patients that recover will show some improvement within 7 days, unless autonomic abnormalities are noted, which are poor prognostic indicators. Median length of hospitalization has been reported to be 13 days (range 6 to 42 days). One study estimated the mortality rate to be approximately 18% in affected dogs. Dogs with surgical wounds manifest a more severe clinical course than those with external wounds, and young dogs are also more likely to develop more severe treatment. There is no documented association between earlier wound treatment, antibiotic administration, or antitoxin administration and either progression of signs or survival. A prospective trial will be necessary in the future to further investigate the value of these therapeutic options. A full recovery may not be possible in at least 15% of dogs that survive, but continued improvement may be seen for 3 to 5 months.[11]

102.8 SUGGESTED FURTHER READING*

KG Braund: Neurotoxin disorders. In KG Braund (Ed.): *Clinical neurology in small animals: localization, diagnosis and treatment*. 2003, International Veterinary Information Service, Ithaca, NY, *Comprehensive veterinary neurology on-line text that is heavily referenced but practically written.*

ES Coleman: Clostridial neurotoxins: tetanus and botulism. *Comp Cont Educ Small Anim Pract*. **20**, 1998, 1089, *Excellent and easy-to-read review of tetanus in dogs and cats; interesting pathophysiologic comparisons made between it and botulism.*

CE Greene: Tetanus. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. ed 3, 2006, Saunders, St Louis, *A comprehensive, well-referenced chapter covering the aspects of tetanus in companion animals.*

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* See the CD-ROM for a complete list of references

103 Chapter 103 Hepatic Encephalopathy

David Holt, BVSc, DACVS

103.1 KEY POINTS

- Hepatic encephalopathy (HE) is associated with moderate to severe liver insufficiency and may be secondary to a portosystemic shunt(s), end-stage liver disease, or congenital urea cycle enzyme deficiencies.
- The pathophysiology of HE is complex and incompletely understood; however, the importance of elevated levels of ammonia have been reemphasized.
- Symptoms may include depression, dementia, stupor, coma, muscle tremors, motor abnormalities, excessive salivation, and focal or generalized seizures.
- Medical management includes strategies to minimize ammonia absorption from the intestine and control seizure activity, if present.
- Definitive therapy involves correcting underlying causes, such as surgical management of a portosystemic shunt.

103.2 INTRODUCTION

HE comprises a spectrum of neurologic abnormalities associated with moderate to severe liver insufficiency. In dogs and cats, it occurs most commonly with portosystemic shunting of blood. Fulminant hepatic failure is an important cause of HE in humans but is seen less commonly in veterinary medicine. Congenital urea cycle enzyme deficiencies may also lead to HE.

103.3 CAUSES

In dogs and cats, congenital extrahepatic or intrahepatic portal-to-systemic venous communications are the most frequent cause of HE; up to 95% of affected animals demonstrate neurologic symptoms.[1] These communications are generally a single vessel, but multiple extrahepatic[2] and intrahepatic[3] congenital portosystemic shunts have been reported. Hepatic arteriovenous malformations cause portal hypertension, multiple extrahepatic portosystemic shunts, and ascites, and may cause symptoms of HE. In young dogs, hepatic microvascular dysplasia[4] and, rarely, congenital urea cycle deficiencies[5] can also cause symptoms of HE. In older animals, portosystemic shunts develop secondary to portal hypertension that results from chronic liver disease. In cats, hepatic lipidosis often is associated with symptoms of HE. Other causes of chronic and acute hepatic failure that can result in symptoms of HE are discussed in Chapter 127, Hepatic Failure.

103.4 PATHOPHYSIOLOGY

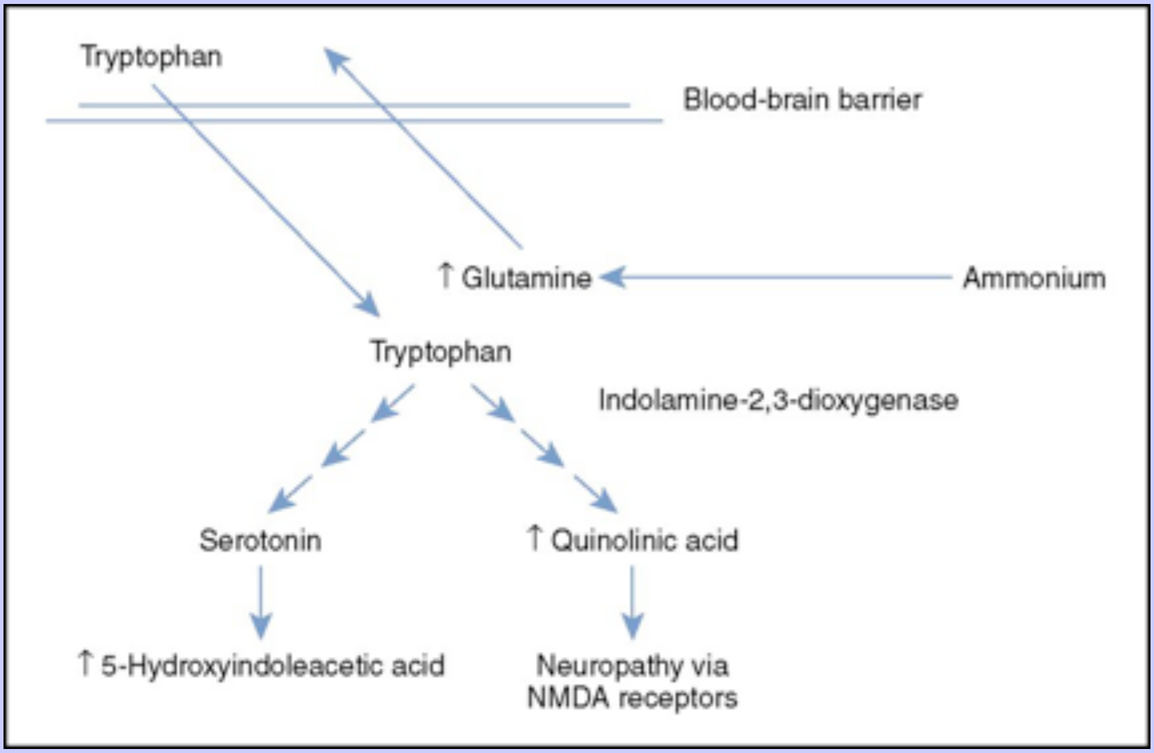
In 1893, Marcel Nencki and Ivan Pavlov described the physiologic consequences of a surgically created, end-to-side portocaval shunt (Eck fistula) and showed that clinical signs in this canine model worsened after a meat meal, linking HE to the concept of "meat intoxication."[6] Ever since this description, HE has been thought of as a condition caused by gut-derived toxins that are not metabolized by a diseased or failing liver. Research over the last century has elaborated on this concept and demonstrated the complexity of this condition. However, recent work on several aspects of HE including cerebrospinal fluid amino acid alterations,[7,8] glutamate neurotoxicity,[9] the generation of reactive oxygen species,[10] and the mitochondrial permeability transition[11] emphasizes the central role of elevated blood ammonia concentrations in animals with HE. Other substances that are considered synergistic with ammonia toxicity include mercaptans, free fatty acids, phenols, and bile salts[12] (see Chapter 127, Hepatic Failure, Table 127-2 for a summary of toxins implicated in HE).

Ammonia is produced in the intestinal tract as the end product of amino acid, purine, and amine breakdown by bacteria, the metabolism of glutamine by enterocytes, and the breakdown of urea by bacterial urease.[13] It is then absorbed into the portal blood and rapidly converted to urea or glutamine in the normal liver. In animals with portosystemic shunting of blood or significant liver disease, high levels of ammonia are present in the systemic circulation. The permeability of the blood-brain barrier to ammonia increases in animals with HE, and experimental studies suggest that HE coma is associated with brain ammonia concentrations in the low millimolar range.[14] These concentrations of ammonia decrease excitatory neurotransmission, in part by down-regulating the N-methyl-D-aspartate (excitatory) receptors,[9] yet at the same time block chloride extrusion from the postsynaptic neuron, decreasing inhibitory neurotransmission.[15]

The brain has no urea cycle; consequently, ammonia in the central nervous system (CNS) is removed by transamination of glutamate into glutamine in astrocytes.[16] Glutamine concentrations in the cerebrospinal fluid are elevated in dogs with HE[8] and often are an accurate indicator of the degree of neurologic dysfunction in humans with HE.[9] Glutamine is exchanged across the blood-brain barrier for tryptophan, leading to increased levels of tryptophan and tryptophan metabolites in the CNS (Figure 103-1).[7] The tryptophan metabolites serotonin and quinolinate are important agonists of inhibitory and excitatory neurotransmission, respectively, although the exact alterations in both of these systems in patients with HE are complex and incompletely understood. Glutamine is also transported from astrocytes into neurons, where it is converted to glutamate.[17] Overstimulation of the N-methyl-D-aspartate receptors by both glutamate and ammonia can cause seizures and neurotoxicity, in part as a result of free radical formation.

γ-Aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the CNS, and alterations of GABA neurotransmission have been proposed as an important component of HE. In spite of several different observations implicating “increased GABAergic tone” in HE, studies have excluded the possibility of increased amounts of GABA in the CNS and changes in the number of GABA receptors or affinity of the receptor for its ligands in patients with HE.[18] It is likely that if increased GABA neurotransmission exists in animals with HE, it is due to increased brain concentrations of endogenous GABA ligands, including endogenous benzodiazepines and neurosteroids. Increased levels of endogenous benzodiazepine receptor ligands have been found in the portal blood and systemic circulation of some dogs with portosystemic shunts.[19] Elevated levels of ammonia and manganese (also seen in liver disease) increase expression of the peripheral-type benzodiazepine receptor, a heterooligomeric protein complex on the outer mitochondrial membrane of astrocytes. Activation of the peripheral-type benzodiazepine receptor increases mitochondrial cholesterol uptake and the synthesis of neurosteroids that may then act on GABA receptors.[20]

Figure 103-1 Diagram of the proposed effect of ammonia on tryptophan metabolism. Ammonia is metabolized to glutamine, which shares an antiport transport mechanism across the blood-brain barrier with tryptophan. An increase in tryptophan transport leads to an increased flux through the serotonin and quinolinic acid pathways.



There is also evidence that amino acid imbalances play a role in patients with HE. Dogs with portocaval shunts have a decreased ratio of branched chain (valine, leucine, isoleucine) to aromatic (phenylalanine, tyrosine, tryptophan) amino acids.[21] Because these classes of amino acids compete for transport across the blood-brain barrier, the increased relative concentration of the aromatic amino acids means that they will be preferentially transported. This leads to an increased synthesis of false neurotransmitters and a reduction in the synthesis of dopamine and norepinephrine. Coma was induced in normal dogs infused with the aromatic amino acids tryptophan and phenylalanine; addition of the branched chain amino acids to the infusion prevented coma.[22]

103.5 CLINICAL SIGNS

The clinical signs associated with HE are often subtle and episodic initially. A new puppy may be mildly lethargic or depressed and first-time owners may not recognize this as abnormal behavior. Other clinical signs may include disorientation, personality change, stupor, pacing, head pressing, "star gazing," amaurotic blindness, coma, and occasionally seizures. In general, signs of CNS depression predominate over signs associated with hyperexcitability. In cats, ptyalism is common, and is often the only clinical sign associated with HE. In dogs, polydipsia and polyuria are also common clinical findings, presumed secondary to hypercortisolemia and the subsequent partial inhibition of vasopressin's action on the renal tubules.[23] Clinical signs of gastrointestinal (GI) (vomiting, anorexia) and urinary tract (stranguria and hematuria secondary to ammonium biurate calculi) disease can also occur in animals with portosystemic shunting of blood. Although these signs are not unique to HE per se, it is important that they alert the veterinarian to investigate the possibility of moderate to severe liver disease.

Clinical signs HE can be precipitated or worsened by the ingestion of a high-protein meal, GI bleeding, systemic infection, and several medications, including narcotics and other anesthetic agents. Other precipitating factors include electrolyte imbalances (hyponatremia, hypokalemia), hypoglycemia, acidosis or alkalosis, and constipation.

103.6 DIAGNOSIS

The diagnosis of HE is made when an animal has clinical signs compatible with the condition and alterations on a biochemical panel and liver function tests confirming moderate to severe liver disease (see Chapter 127, Hepatic Failure). At the same time, none of the clinical signs described are specific for HE and other potential diagnoses, including other metabolic disorders, toxin or drug ingestion, and intracranial lesions, should be excluded. Routine laboratory analysis (complete blood count, biochemical profile, urinalysis) and liver function testing are often indicated. Possible liver function tests include preprandial and postprandial serum ammonia or bile acid levels, ammonia tolerance test (may potentiate seizure activity and therefore us contraindicated in patients with HE), and sulfobromophthalein dye retention test. It is important to note that samples for blood ammonia concentrations are useful only if processed immediately. Canine samples for blood ammonia determination that are stored frozen for any length of time give erroneous results.[24] Additional diagnostic testing that might be necessary include rectal portal scintigraphy and liver histopathology.

103.7 TREATMENT

See Chapter 127, Hepatic Failure, Table 127-3 for a summary of treatments.

Animals that have or develop focal or generalized seizures will require immediate intervention to stop them (see Chapters 98 and 186, Seizures and Status Epilepticus and Anticonvulsants, respectively). The use of diazepam (Valium) is controversial because of the possibility of endogenous benzodiazepine agents (see Pathophysiology earlier in this chapter). The dosage is typically 0.5 mg/kg IV. Alternatively, the seizure activity may be managed with propofol (0.5 to 1 mg kg IV bolus, then 0.05 to 0.1 mg/kg/min constant rate infusion). Mannitol therapy may also prove beneficial if cerebral edema is present (0.5 to 1 g/kg IV over 30 minutes). Potassium bromide can be administered in an attempt to prevent further seizure activity by loading the animal initially with 400 to 600 mg/kg q24h divided into 4 doses on day 1, then maintenance therapy at 40 mg/kg q24h PO or rectally. Sodium bromide has been suggested as a parenteral antiepileptic formulation in dogs and cats, although there are few data to support its clinical use. The drug is generally administered at 15% of the potassium bromide dosage, including the loading dose on day 1. Phenobarbital may also be used as a parenteral antiepileptic, and a loading dose is typically given on day 1 at 16 mg/kg IV divided into 4 doses, followed by 2 to 4 mg/kg IV q12h thereafter. Both the bromide drugs and phenobarbital may lead to excessive sedation, and close monitoring is therefore essential.

In animals with hepatic coma or seizures, any predisposing factor should be treated. For example, in the case of benzodiazepine sedation, flumazenil (0.02 mg/kg IV) is administered. Intubation of comatose animals or those recovering from seizure activity may be necessary to protect the airway from aspiration and to maintain ventilation. IV fluids are often necessary, but the animal's serum albumin, glucose, electrolyte, and acid-base status should be evaluated carefully before and during administration. Affected animals are often hypoproteinemic and hypoglycemic; alkalosis increases ammonia diffusion into the CNS and hypokalemia stimulates renal ammonia production. Colloid administration (synthetic or fresh frozen plasma) and potassium and glucose supplementation are often necessary. Should a transfusion be necessary, fresh whole blood or packed red blood cells are used, because storage of red blood cell products increases the ammonia concentration.[25] A lactulose enema is administered to prevent ammonia production in, and absorption from, the colon. Lactulose (β-galactosidofructose) is a nonabsorbable disaccharide that exerts an osmotic cathartic action. In addition, intestinal bacteria hydrolyze lactulose-producing organic acids that lower colonic pH. Acidification traps ammonia in its NH_4^+ form, preventing absorption by nonionic diffusion, and also results in the net movement of ammonia from the blood into the bowel lumen.

Fulminant hepatic failure is uncommon in animals but may be fatal. Death in humans with fulminant hepatic failure is often associated with cerebral edema, hemorrhage, and sepsis. Therapy is similar to that described for hepatic coma and seizures. Assisted ventilation is used to prevent hypoventilation and minimize changes in intracranial pressure. Twenty-five percent mannitol (0.5 to 1 g/kg IV) is administered to minimize cerebral edema. Glucose is supplemented as necessary. Animals with fulminant hepatic failure may be coagulopathic, and fresh frozen plasma (10 to 20 ml/kg IV) is administered to supplement coagulation factors, if needed. Bacterial cultures (blood, urine) are obtained and broad-spectrum antibiotics are administered in animals with suspected bacterial sepsis (see Chapter 106, Sepsis). 440 441

General treatment goals for stable animals with HE or those that have been stabilized after treatment for emergent conditions include reducing ammonia levels, decreasing GABA, and lowering endogenous benzodiazepines. Clinical signs of HE can typically be treated with diet modification, oral administration of lactulose, and antibiotic therapy. The diet should be moderately protein restricted (14% to 17% protein on a dry matter basis in dogs; 30% to 35% protein in cats) and high in carbohydrates. The protein should be of high quality and have a high level of branched chain amino acids. The diet should be a low-residue, easily digestible food to minimize the amount of material reaching the colon. It must contain adequate amounts of arginine for cats, because this is an essential amino acid that is necessary for the urea cycle.

Lactulose is an osmotic cathartic that increases transit time through the GI tract, thereby decreasing the availability of glutamine sources (ingested and endogenous) for metabolism. The pH of the intestinal contents is also reduced, which decreases the numbers of urease-producing colonic bacteria and traps ammonia within the GI tract as ammonium ions. Lactulose (1 to 3 ml/10 kg q6-8h) is administered orally or rectally (diluted to 30% with warm water and retained for 30 minutes), and the dosage rate and interval are titrated to produce two to four moderately soft stools daily.

Antibiotics are administered to decrease numbers of urease-producing bacteria in the intestines. Neomycin sulfate (20 mg/kg PO q6-8h) is generally considered nonabsorbable, but it should be avoided in animals with concurrent renal disease. Metronidazole (10 to 20 mg/kg PO or IV q12h) is a reasonable alternative, but neurotoxicity may occur more commonly in animals with hepatic disease. Rifaximin is a commonly used antibiotic for the treatment of HE in humans, but its use in small animals is limited at this time. The effect of long-term antibiotic therapy on the intestinal flora of dogs and cats is not clear. Because the therapeutic effect of lactulose depends on its metabolism by colonic bacteria, the benefit of combined lactulose and antibiotic therapy is open to question in small animals. Although the two treatments often are considered synergistic, oral neomycin inhibits lactulose metabolism in 25% to 30% of human patients.

Enemas have also been used to decrease the colonic bacterial numbers and substrates. The following types of enemas have been recommended:

- Warm water enemas at 10 ml/kg q4-6h until signs improve
- Lactulose enemas at 5 to 15 ml diluted 1:3 with warm water and administered q6-8h
- Neomycin enemas at 15 to 20 ml of 1% solution q8-12h
- Metronidazole enemas at 7.5 mg/kg (systemic dose) mixed with water q12h
- Povidone-iodine (Betadine) enemas given by diluting 1:10 with warm water and giving 10 ml/kg q8h and flushing out with warm water after 10 to 15 minutes
- Activated charcoal enemas using the liquid suspension q8h (can be administered and retained in crisis)
- Vinegar enemas made by diluting the vinegar 1:4 with warm water and administering at 10 ml/kg q8h

Other therapies that have been studied in humans but not companion animals include ornithine aspartate, intestinal repopulation with lactose fermenting, non–urease-containing bacteria, zinc supplementation, branched chain amino acid solutions, and flumazenil and levodopa administration.[26] Inhibitors of the glutamine synthetase enzyme and serotonin receptor antagonists have been associated with a high rate of side effects and are not used for treatment of clinical HE in humans.

In cases of HE secondary to portosystemic shunting of blood, correcting the portosystemic shunt surgically often resolves the clinical signs of HE permanently in dogs. In cats, a variable percentage may have residual or recurrent neurologic signs.[27] Treatment of extrahepatic shunts usually involves either complete suture ligation or placement of either an ameroid ring or cellophane band to occlude the shunting vessel more slowly. Intrahepatic shunts are treated either surgically or with interventional radiographic techniques. All of these procedures require general anesthesia; the metabolism of anesthetic agents and their effects on the CNS are far from clear in animals with HE. Although controlled clinical trials are lacking, general opinion favors a period of medical treatment to stabilize animals with HE before anesthesia induction.

Animals with liver insufficiency commonly experience clinical or subclinical GI hemorrhage, and the digested blood serves as another protein source protein that may cause or contribute to HE. It is therefore recommended that these animals receive GI protectant therapy (see Chapter 181, Gastrointestinal Protectants). Drugs such as famotidine (0.25 to 1 mg/kg PO or IV q12-24h), omeprazole (0.5 to 1 mg/kg/day PO q12h), misoprostol (2 to 3 µg/kg PO q8h), and sucralfate (0.25 to 1 g/25 kg PO q6-8h) are commonly used.

103.8

SUGGESTED FURTHER READING*

J Albrecht, EA Jones: Hepatic encephalopathy: Molecular mechanisms underlying the clinical syndrome. *J Neurol Sci*. **170**, 1999, 138, *A comprehensive review of the current concepts of molecular changes thought to occur in the central nervous system in HE*.

LR Aronson, RC Gacad, K Kaminsky-Russet, et al.: Endogenous benzodiazepine activity in the peripheral and portal blood of dogs with congenital portosystemic shunts. *Vet Surg*. **26**, 1997, 189, *Article describing that endogenous benzodiazepine levels are elevated in the portal and systemic circulation in some dogs with spontaneous portosystemic shunts*.

RF Butterworth: Neurotransmitter dysfunction in hepatic encephalopathy: new approaches and new findings. *Metab Brain Dis*. **16**, 2001, 55, *A review of CNS changes in HE that discusses the potential roles of manganese, the "peripheral-type" benzodiazepine receptor, and neurosteroids*.

J Butterworth, CR Gregory, LR Aronson: Selective alterations of cerebrospinal fluid amino acids in dogs with congenital portosystemic shunts. *Metab Brain Dis*. **12**, 1997, 299, *Describes abnormal concentrations of glutamate and glutamine in the cerebrospinal fluid of dogs with spontaneously occurring portosystemic shunts*.

DS Dimski: Ammonia metabolism and the urea cycle: functional and clinical implications. *J Vet Intern Med*. **8**, 1994, 73, *A review of ammonia metabolism and the urea cycle*.

E Konsenko, N Venediktova, Y Kaminsky, et al.: Sources of oxygen radicals in brain in acute ammonia intoxication in vivo. *Brain Res*. **981**, 2003, 193, *Describes the formation of potentially toxic oxygen free radicals induced by ammonia in an experimental rat model of HE*.

* See the CD-ROM for a complete list of references

104 Chapter 104 Vestibular Disease

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104.1 KEY POINTS

- Patients with vestibular disease have dysfunction of the vestibular system and are often presented for treatment on an acute emergency basis.
- The vestibular system is comprised of a peripheral component within the structures of the inner ear and central components in the brain stem and cerebellum.
- The common clinical signs of vestibular disease include head tilt, ataxia, and nystagmus.
- Peripheral vestibular disease can be accompanied by Horner's syndrome and facial nerve paresis.
- Central vestibular disease typically is accompanied by loss of proprioceptive and motor function, in addition to multiple cranial nerve deficits and mentation changes.
- The differential diagnosis for the cause of vestibular disease depends on the localization of the lesion to the peripheral or central components.
- Treatment of vestibular disease is determined by the underlying etiology, but supportive care is extremely important to the speed of individual patient compensation.

104.2 INTRODUCTION

Dogs and cats have the ability to control posture and movements of the body and eyes relative to the external environment. The vestibular system mediates these activities through a network of receptors and neural elements. Disease leading to dysfunction of the vestibular system can lead to dramatic signs of disequilibrium. The investigation, treatment, and prognosis of the cause of the disequilibrium can differ depending on whether the peripheral or central components of the system are affected.

This chapter outlines the relevant anatomy of the vestibular system and how this influences the clinical signs of its dysfunction, in addition to the diseases that are most commonly responsible for the acute onset of clinical signs constituting an emergency.

104.3 NEUROANATOMY OF THE VESTIBULAR SYSTEM

The vestibular system can be divided into peripheral components located in the inner ear and central nervous system (CNS) components. Three major CNS areas receive projections from the peripheral sensory receptors of the vestibular system: the cerebral cortex, the spinal cord, and the cerebellum. The projection to the cerebral cortex incorporates extensions to the extraocular muscles.

104.3.1 Nerve Pathways to the Extraocular Muscles

Two neurons make up the pathway responsible for the sensory input of the head to the cerebral cortex (Figure 104-1).

104.3.1.1 Neuron 1

The cell location for the first neuron is within the vestibular ganglion of the eighth cranial or vestibulocochlear nerve, and the axon projects into the ipsilateral vestibular nuclei. These neurons receive input from the vestibular receptors in the membranous labyrinth contained within a bony labyrinth in the petrous temporal bone. The sensory neurons are incorporated into the vestibulocochlear nerve, which leaves the petrous temporal bone via the internal acoustic meatus, along with the facial nerve, and enters the medulla of the brain stem.[1]

104.3.1.2 Neuron 2

The cell location for the second neuron is in the vestibular nuclei, which are situated in the medulla oblongata. From these nuclei, axons travel in the medial longitudinal fasciculus within the brain stem. The ascending axons within the fasciculus give off numerous side branches to the motor nuclei of cranial nerves III, IV, and VI, thereby providing coordinated conjugated eyeball movements associated with changes in position of the head. Some axons project from the nuclei into the reticular formation and go on to provide afferents to the vomiting center located there.[1]

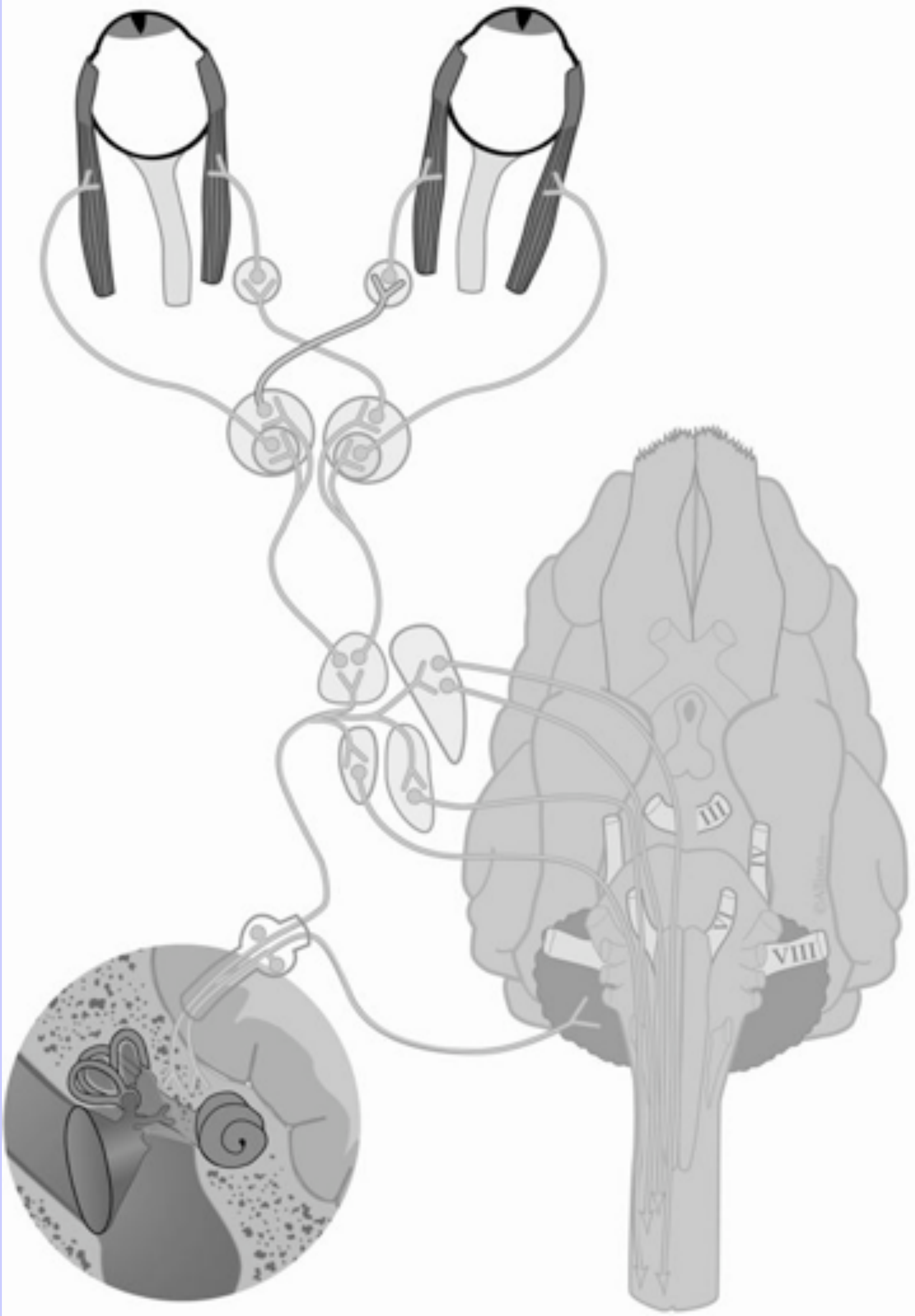
104.3.2 Nerve Pathways to the Spinal Cord

The vestibulospinal tract descends from the vestibular nuclei and projects mainly onto α-neurons or extensor motor neurons throughout the length of the cord via interneurons in the ventral grey column.[1] This pathway is strongly facilitatory to the ipsilateral alpha and gamma motor neurons to extensor muscles.

104.3.3 Nerve Pathways to the Cerebellum

The vestibular nuclei project directly to the cortex of the ipsilateral flocculonodular lobe (the flocculus of the hemisphere and the nodulus of the caudal vermis), as well as the fastigial nucleus of the cerebellum.[1] The return pathway from a cerebellar nucleus to the vestibular nuclei is also ipsilateral; this is an extremely large projection, providing the cerebellum with a strong influence over the activity of the vestibular nuclei. These pathways between the cerebellum and the vestibular nuclei travel in the caudal cerebellar peduncle.

Figure 104-1 Diagrammatic overview of the neuroanatomy of the vestibular system. From Platt S, Olby N, editors: *Manual of canine and feline neurology,* ed 3, Gloucester, 2004, British Small Animal Veterinary Association.



104.4 CLINICAL SIGNS

Unilateral vestibular disease produces asymmetric signs, often on or toward the side of the disease. The most common clinical signs of vestibular disease are head tilt, nystagmus, and ataxia; these may be single entities or a combination of signs.[2] The primary aim of the neurologic examination is to determine if these vestibular signs are due to a peripheral vestibular system (inner ear) disease or a central vestibular system (brain stem and cerebellum, or both) disease. Localization of the disease determines the most appropriate diagnostic tests, the differential diagnoses, and the prognosis.

The essential determination of whether these signs are due to a peripheral or central disease may be possible by the identification of associated neurologic signs that are present only with central disease.[2] Signs of central vestibular syndrome suggest damage to the brain stem and are not present in patients with inner ear disease unless there has been extension of the inner ear disease into the brain stem, such as can be seen with otitis media, otitis interna, and neoplasia.[3]

104.4.1 Specific Signs of Vestibular Dysfunction

Signs of vestibular dysfunction are outlined in Table 104-1.

104.4.1.1 Head Tilt

Loss of equilibrium is most commonly represented clinically as a head tilt that may be present with either central or peripheral vestibular disease. The head tilt is always toward the side of the lesion with peripheral disease but may be toward either side with central disease. When the head tilt is opposite to the side of the lesion, it is termed *paradoxical*. [2] This can be seen with lesions of the flocculonodular lobe of the cerebellum or the supramedullary part of the caudal cerebellar peduncle, with sparing of the vestibular nuclei in the rostral medulla; the head tilt often is accompanied by ipsilateral cerebellar signs, paresis, and proprioceptive deficits.[3]

Table 104-1 Neurologic Examination Findings in Animals With Peripheral and Central Vestibular Dysfunction

Clinical Signs	Peripheral Vestibular Disease	Central Vestibular Disease
Head tilt	Toward the lesion	Toward the lesion, or away from the lesion with paradoxical disease
Spontaneous nystagmus	Horizontal or rotatory with the fast phase away from the side of the lesion Rarely positional	Horizontal, rotatory, vertical and or positional with the fast phase toward or away from the lesion
Paresis and proprioceptive deficits	None	Commonly ipsilateral to the lesion
Mentation	Normal to disoriented	Depressed, stuporous, obtunded, or comatose
Cranial nerve deficits	Ipsilateral CN VII deficit	Ipsilateral CN V, VII, IX, X, and XII
Horner's syndrome	Common ipsilateral to the lesion	Uncommon
Head tremors	None	Can occur with concurrent cerebellar dysfunction
Circling	Infrequent but can be seen toward the side of the lesion	Usually toward the side of the lesion

CN, Cranial nerve.

Bilateral peripheral vestibular disease does not produce asymmetric lesions such as a head tilt. A characteristic side-to-side head movement is seen instead.

104.4.1.2

Nystagmus

Pathologic or spontaneous nystagmus is an involuntary rhythmic oscillation of both eyes, occurs when the head is still, and is a sign of altered vestibular input to the neurons that innervate the extraocular eye muscles.[2] This is in contrast to physiologic nystagmus, which can be induced in normal animals. Pathologic nystagmus may be horizontal, rotatory, or vertical. Vertical nystagmus implies a central vestibular lesion but it is not a definitive localizing sign. If nystagmus of any direction is induced only when the head is placed in an unusual position, it is known as *positional nystagmus,* which may be more common with, but not specific for, central disease; this term may also refer to nystagmus that changes its predominant direction with altered head positions.[2]

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Nystagmus occurs with the fast phase away from the damaged side and with the slow phase commonly directed toward the affected side. In acute and or aggressive nystagmus, the eyelids may be seen to contract at a rate corresponding to that of the nystagmus. Nystagmus may disappear with chronicity of the underlying lesion, particularly with peripheral disease, but its presence usually indicates an active disease process within the vestibular apparatus. Animals with bilateral vestibular disease do not have pathologic or physiologic nystagmus.[4]

104.4.1.3 Ataxia

Ataxia is a failure of muscular coordination or an irregularity of muscle action. It is generally associated with a cerebellar, vestibular, or proprioceptive pathway abnormality. Animals with vestibular dysfunction assume a wide-based stance and may lean or drift toward the side of a lesion if the dysequilibrium is not too severe.[4]

104.4.2 Signs That May Be Associated With Vestibular Dysfunction

104.4.2.1 Facial Paresis, Paralysis, and Hemifacial Spasm

Cranial nerve VII, the facial nerve, is commonly involved in the same disease processes that cause peripheral vestibular disease.[5] The resulting signs are those of facial paresis, paralysis or, more rarely, spasm.

104.4.2.2 Horner's Syndrome

Horner's syndrome (miosis, ptosis, enophthalmos, and protrusion of the third eyelid) of the ipsilateral eye may be present with either middle or inner ear disease causing peripheral vestibular dysfunction.[6] This association is seen because the vagosympathetic trunk synapses in the cranial cervical ganglion deep to the tympanic bulla. Horner's syndrome rarely is associated with central vestibular disease.[1]

104.4.2.3 Hemiparesis or Tetraparesis

Paresis suggests abnormal neurologic function (weakness) without complete paralysis, which implies that some voluntary motion remains. Locomotion is thought to be initiated in the brain stem of animals, so paresis usually is seen with any lesion within the neuraxis caudal to the level of the red nucleus in the midbrain.[3] With unilateral focal central vestibular diseases, paresis of the ipsilateral limbs (hemiparesis) may be seen if the motor pathways in the medulla oblongata are also affected. A large lesion or multifocal lesions may cause an asymmetric tetraparesis. Paresis does not occur with peripheral vestibular disease.

104.4.2.4 Altered Mental State

Disorders causing central vestibular dysfunction may be accompanied by altered mentation. The reticular activating system of the brain stem facilitates the alert and awake state in animals.[1] Damage to this area may cause the animal to become disoriented, stuporous, or comatose.[3] Although peripheral vestibular disease will not cause stupor or coma, it may cause disorientation, which can make the assessment of the animal's mental status difficult.

104.4.2.5 Multiple Cranial Nerve Dysfunction

Central vestibular syndrome may be accompanied by other cranial nerve dysfunction as well. Clinical signs can include ipsilateral facial hypalgesia, atrophy of the masticatory muscles, reduced jaw tone, facial paralysis, tongue weakness, and loss of the swallow or gag reflex.

104.4.2.6 Circling, Leaning, and Falling

With unilateral vestibular dysfunction, dogs or cats may exhibit an ipsilateral reduction in extensor tone, and contralateral hypertonicity, causing them to lean, fall, and circle toward the side of the lesion.[2] Falling may occur when the animal shakes its head if there is aural irritation.

104.4.2.7 Decerebellate Posturing

In severe forms of central vestibular dysfunction, the underlying disease may also cause decerebellate posturing or rigidity; this is characterized by opisthotonus with thoracic limb extension, normal mentation, and flexion of the pelvic limbs.[3] This posture can occur intermittently and be accompanied by vertical nystagmus, the combination being confused by owners as some type of seizure activity. Dorsiflexion of the neck will sometimes elicit this posture.

104.4.2.8 Vomiting

The vomiting center is located within the reticular substance of the medulla, and there are direct connections to it from the vestibular nuclei.[1] Vomiting may be seen in animals affected acutely by vestibular disease.[2]

104.5 DIFFERENTIAL DIAGNOSIS OF ACUTE VESTIBULAR DISEASE

Tables 104-2 and 104-3 outline the overall etiology and infectious etiologies, respectively of acute vestibular disease.

104.6 DIAGNOSTIC APPROACH TO THE ANIMAL WITH ACUTE VESTIBULAR DISEASE

The approach to an animal with vestibular disease can depend on whether a peripheral or central lesion is suspected (Figure 104-2). To determine this, a complete history and a thorough physical and neurologic examination are essential.

The following tests can be performed in sequence, advancing in expense and invasive nature until satisfactory information is acquired. All of the tests may be necessary if central disease is suspected, whereas cerebrospinal fluid (CSF) analysis and advanced imaging may not be necessary if peripheral disease is responsible for the vestibular dysfunction.

104.6.1 Minimum Database

Hematology, a comprehensive serum biochemistry, thyroid function analysis, urinalysis with culture and sensitivity, thoracic radiographs, and abdominal ultrasonography or radiographs should be analyzed in all cases of acute vestibular dysfunction to evaluate the patient for multisystemic or concurrent disease.

104.6.2 Otoscopy and Pharynx Examination

General anesthesia is necessary to thoroughly examine the ears and pharynx for abnormalities such as exudates
and soft tissue masses. Both ears should be examined with an otoscope. The tympanum should be examined for 444
color, texture, and integrity; it is usually dark gray or brown in cases of otitis. An intact tympanum does not rule 445
out otitis media, and diagnosing otitis media on the sole basis of a ruptured tympanum is also unreliable.[5]

Table 104-2 Etiologies of Peripheral and Central Vestibular Diseases[1]

	Specific Diseases	
Disease Mechanism	**Peripheral Disease**	**Central Disease**
Degenerative	—	Cerebellar cortical abiotrophy Lysosomal storage diseases
Anomalous	Congenital vestibular disease	Hydrocephalus Intracranial intraarachnoid cysts
Nutritional	—	Thiamine deficiency
Neoplasia	Squamous cell carcinoma Fibrosarcoma Osteosarcoma Ceruminous gland or sebaceous gland adenocarcinoma	Meningioma Oligodendroglioma Medulloblastoma Lymphoma Extension of middle ear neoplasia Metastasis
Inflammatory or infectious	Bacterial otitis interna or labyrinthitis Cryptococcosis Nasopharyngeal polyps (cuterebral larval migration)	See Table 104-3
Idiopathic	Idiopathic vestibular syndrome	—
Toxic	Aminoglycosides Furosemide Chlorhexidine 10% Fipronil solution (aural administration)	Metronidazole Lead
Traumatic	Iatrogenic: External middle ear flushing or bulla osteotomy Bulla fracture or hemorrhage	Head trauma
Vascular	—	Infarction or hemorrhage Feline ischemic encephalopathy Cuterebral larval migration

104.6.3 Radiography

Radiography is useful for evaluating the osseous tympanic bulla. Skull radiographs should be performed under general anesthesia to achieve adequate positioning. This may not always be possible, particularly in the trauma patient. Lateral, dorsoventral, or ventrodorsal, lateral-20 degree ventral-laterodorsal oblique, and rostral-30 degree ventral-caudodorsal open-mouth oblique radiographs are advised for the assessment of tympanic bulla.[7]

Table 104-3 Infectious and Inflammatory Central Nervous System Disorders That May Cause Vestibular Dysfunction [1]

Class of Etiologic Agent	Disease
Viral	Feline infectious peritonitis Feline immunodeficiency virus Feline leukemia virus Rabies Pseudorabies Borna disease virus Distemper virus
Protozoal	Toxoplasmosis, neosporosis Encephalitozoonosis
Bacterial	Aerobes Anaerobes
Rickettsial	*Rickettsia rickettsii* *Ehrlichia* spp
Fungal	Cryptococcosis Blastomycosis Histoplasmosis Coccidioidomycosis Aspergillosis Phaeohyphomycosis
Parasitic	*Angiostrongylus vasorum* Cuterebral larval myiasis Dirofilaria immitis
Agent unknown	Nonsuppurative meningoencephalomyelitis (presumed viral) Eosinophilic meningoencephalitis Granulomatous meningoencephalitis Necrotizing meningoencephalitis (Pug, Maltese Terrier) Necrotizing leukoencephalitis (Yorkshire Terrier)

104.6.4 Myringotomy

Myringotomy is the deliberate puncture or incision of an intact, although not necessarily healthy, tympanic membrane.[8] Needle puncture and subsequent aspiration through the ventrocaudal part of the tympanic membrane allows for collection of fluid from the tympanic cavity for cytologic examination and microbial culture and sensitivity testing.

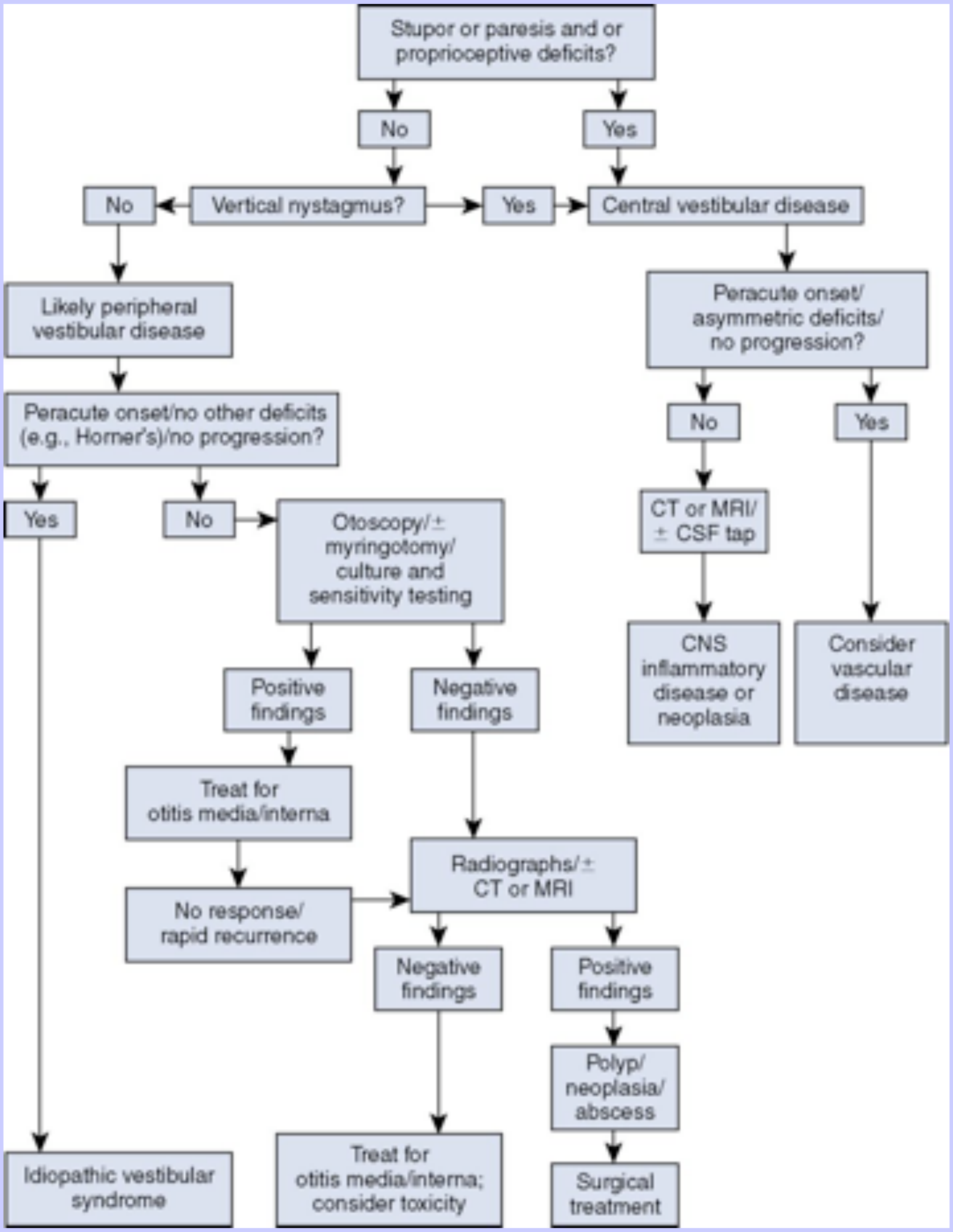
104.6.5 Brain Stem Auditory Evoked Potentials

Brain stem auditory evoked potentials testing, also known as *brain stem auditory evoked response testing,* can be used to assess the integrity and function of the peripheral and central auditory pathways, which allows for indirect evaluation of the vestibular pathways because of their close association.[9] Brain stem auditory evoked potentials are recordings of sound-evoked electrical changes in portions of the auditory pathway between the cochlea and the auditory cortex. Because of the level of patient cooperation required, sedation or a light plane of general anesthesia is often needed for this test to be performed and interpreted properly.[9]

104.6.6 Cerebrospinal Fluid Analysis

CSF analysis is a useful adjunctive test for determining the cause of central vestibular disease, although results 445 are rarely specific. Although serum and CSF antibody titers have been used previously to diagnose infectious 446 diseases, polymerase chain reaction analysis of CSF can now be performed in specialized laboratories to evaluate for the presence of infectious antigens rather than antibody titers.[10] The risk of iatrogenic CNS trauma or cerebellar herniation following cisterna magna puncture with space-occupying lesions should not be underestimated. It is preferable to obtain advanced imaging studies of the brain (see Advanced Imaging section next in this chapter) before performing CSF tap, especially if a caudal fossa lesion is suspected.

Figure 104-2 Algorithm detailing the approach to the patient with acute vestibular disease. *CNS,* Central nervous system; *CSF,* cerebrospinal; *CT,* computed tomography; *MRI,* magnetic resonance imaging.


Stupor or paresis and or proprioceptive deficits?
No
Yes
No
Vertical nystagmus?
Yes
Central vestibular disease
Likely peripheral vestibular disease
Peracute onset/ asymmetric deficits/ no progression?
Peracute onset/no other deficits (e.g., Horner's)/no progression?
No
Yes
Yes
No
Otoscopy/± myringotomy/ culture and sensitivity testing
CT or MRI/ ± CSF tap
Positive findings
Negative findings
CNS inflammatory disease or neoplasia
Consider vascular disease
Treat for otitis media/interna
Radiographs/± CT or MRI
No response/ rapid recurrence
Negative findings
Positive findings
Polyp/ neoplasia/ abscess
Idiopathic vestibular syndrome
Treat for otitis media/interna; consider toxicity
Surgical treatment

104.6.7 Advanced Imaging

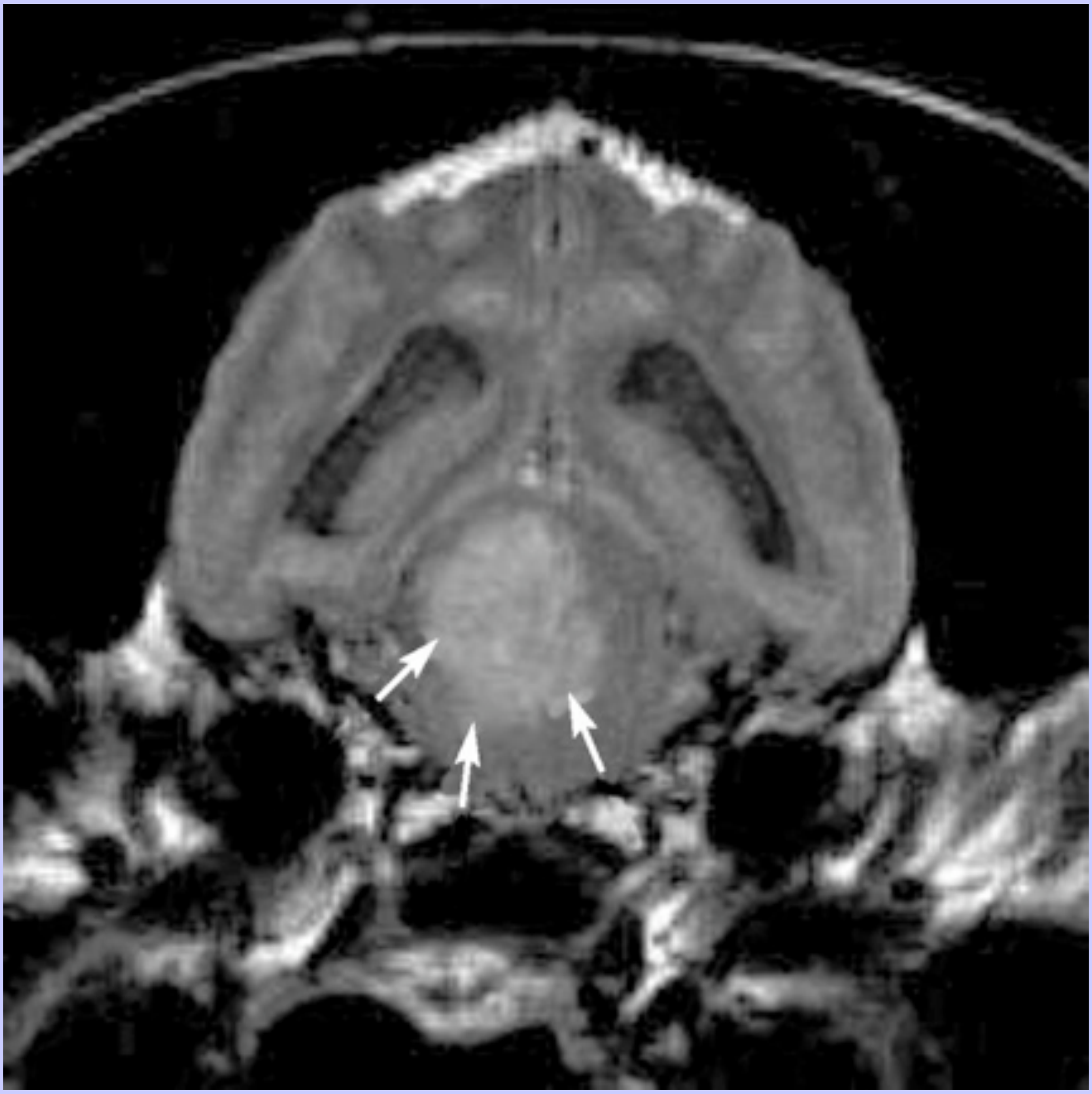
Computed tomography (CT) and magnetic resonance imaging (MRI) have revolutionized the diagnosis of vestibular diseases. CT evaluation of the peripheral vestibular system is particularly useful if radiographs have not determined an underlying cause, if nasopharyngeal polyps and neoplasia are considerations, or if the animal is a potential surgical candidate. CT evaluation for central vestibular diseases may be less helpful because of the artifacts relating to the density of the petrous temporal bones surrounding the medulla (e.g., beam hardening).[11]

MRI of the peripheral and central vestibular systems provides excellent multiplanar soft tissue resolution when compared with CT.[11] The improved soft tissue contrast provided by this modality allows better assessment of neoplastic and inflammatory conditions that result in vestibular dysfunction (Figure 104-3). A typical MRI study consists of T1-weighted, T2-weighted, and proton density–weighted transverse images made before contrast medium administration.[11] Postcontrast sequences have been recommended if a mass is present in the tympanic bulla or the external ear canal.

104.7 TREATMENT AND PROGNOSIS

The damaged vestibular system can compensate over time with central reprogramming of eye movements and postural responses, as well as reliance on visual and other sensory input that replaces lost vestibular input.[2] If the underlying disease process can be targeted, the prognosis for a functional recovery can be good. Residual signs, such as a head tilt, are always possible. Recurrences can occur at times of stress, recurrent disease, or following anesthesia.

Figure 104-3 Transverse T2-weighted fluid-attenuated inversion recovery magnetic resonance study of a 4-year-old mixed breed dog with central vestibular disease and multiple cranial nerve involvement. A large irregular lesion hyperintense to the surrounding brain stem is identified *(arrows)*. Pathologic examination confirmed granulomatous meningoencephalomyelitis.



Supportive care can be essential, especially because these animals are frequently anorexic; feeding tubes and fluid therapy can be vital initially until the patient can self-maintain. Vomiting, salivation, and nausea associated with vestibular disease can be treated with antiemetic medications. Drugs commonly used include the phenothiazine derivative chlorpromazine (0.2 to 0.5 mg/kg SC q8h), serotonin receptor antagonists dolasetron (0.6 to 1 mg/kg SC, IV, or PO q24h) and ondansetron (0.1 to 0.1 mg/kg PO q12-24h or 0.1 to 0.5 mg/kg IV slowly q6-12h), metoclopramide, an antidopaminergic serotonin receptor antagonist and chemoreceptor trigger zone inhibitor (0.1 to 0.5 mg/kg IV, SC, or PO q6h or as an IV infusion of 1.1 to 2.2 mg/kg q24h), or the antihistamines diphenhydramine (2 to 4 mg/kg PO or IM q8h) and meclizine (12.5 mg PO q24h) (see Chapter 182, Antiemetics).[2]

104.8 SUGGESTED FURTHER READING*

RS Bagley: Recognition and localization of intracranial disease. *Vet Clin North Am Small Anim Pract*. **26**, 1996, 667, *A review chapter that documents the symptoms expected with lesions in the various regions of the intracranial neuroanatomy*.

LB Cook: Neurologic evaluation of the ear. *Vet Clin North Am Small Anim Pract*. **34**, 2004, 425, *An article that reviews neurologic dysfunction commonly associated with diseases of the ear and differentiating these symptoms from central disease*.

WB Thomas: Vestibular dysfunction. *Vet Clin North Am Small Anim Pract*. **30**, 2000, 227, *A comprehensive review of vestibular disease in dogs and cats*.

* See the CD-ROM for a complete list of references

105 Chapter 105 Cerebrospinal Fluid Sampling

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105.1 KEY POINTS

- Cerebrospinal fluid (CSF) analysis can rapidly provide information that may be useful in making a diagnosis, deciding on a treatment protocol or further diagnostic tests, and monitoring response of central nervous system (CNS) disease to medical treatment.
- The most common indication for CSF analysis in the emergency or intensive care unit setting is suspicion of infectious or inflammatory disease of the CNS.
- In collecting CSF, correct patient positioning and a good understanding of regional anatomy are essential.
- CSF findings uncommonly yield a definitive diagnosis and should be interpreted in light of the patient history, neurologic signs, and other diagnostic results. In addition, they may be normal in spite of significant CNS disease.
- Risks versus benefits of a CSF collection should be considered carefully in patients with elevated intracranial pressure.
- CSF cell counts and cytology study may be done in-house with minimal investment in equipment and will give the emergency clinician the most useful information for making a diagnosis.

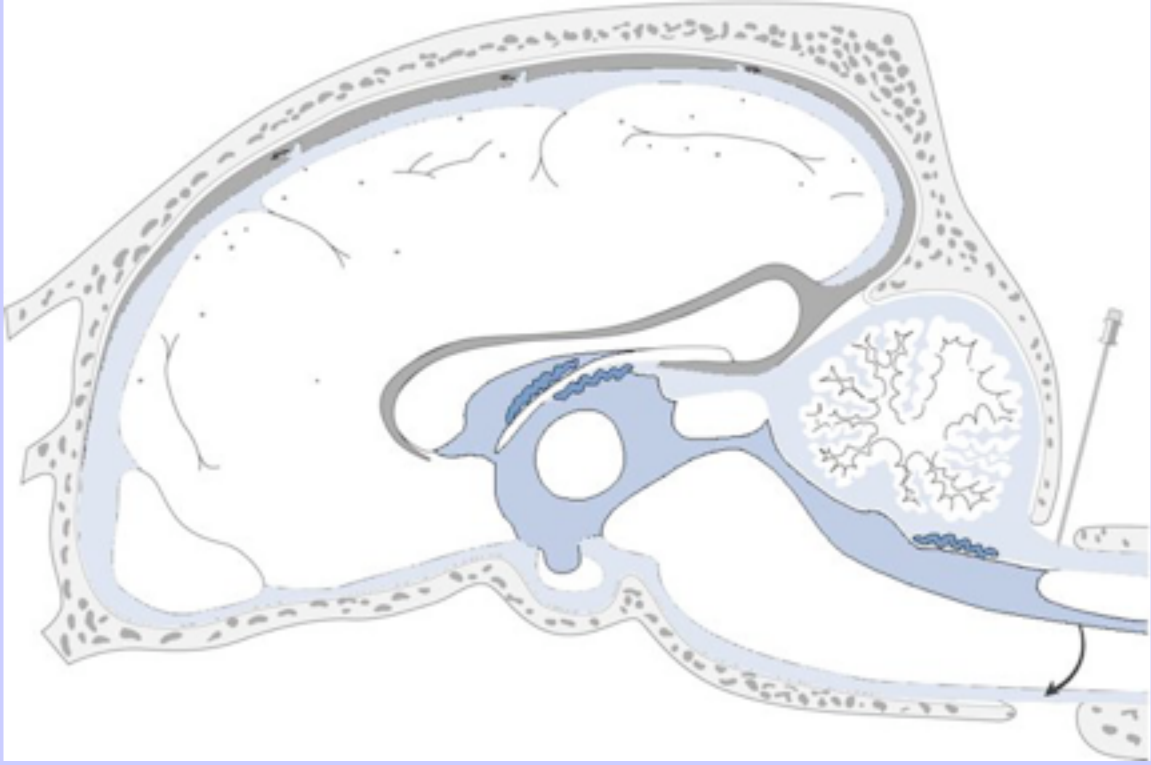
105.2 INTRODUCTION

Cerebrospinal fluid (CSF) collection and analysis may provide rapid information to the clinician investigating a disease affecting the central nervous system (CNS).[1,2] It is particularly useful for confirming the presence of inflammatory and infectious diseases affecting the brain, spinal cord, or nerve roots, especially when the meninges are involved.[1-3] However, CSF analysis should be considered only after an accurate history, physical, and neurologic examination has localized a lesion to the CNS and a logical list of differential diagnoses has been considered carefully.[1,2] In most situations, the results of a CSF analysis provide the clinician with a “piece of the puzzle” that must be used in conjunction with the results of other diagnostic tests, especially magnetic resonance imaging (MRI), to arrive at a correct diagnosis.

105.3 CEREBROSPINAL FLUID FORMATION AND FUNCTIONS

The presence of CSF in the subarachnoid space reduces mechanical trauma to the nervous tissue and serves to remove the products of brain metabolism (Figure 105-1). It is also an intracerebral transport medium for nutrients, neuroendocrine substances, and neurotransmitters.[4] Most CSF is formed by the choroid plexus in the ventricles via ultrafiltration of plasma and the active transport of selected substances across the blood-brain barrier.[4] The CSF flows caudally through the ventricular system; the majority exits via the fourth ventricle to circulate cranially around the brain and caudally around the spinal cord in the subarachnoid spaces.[4] Absorption of CSF occurs primarily through the arachnoid villi that penetrate the major dural venous sinuses in the cranium.[4]

Figure 105-1 Cerebrospinal fluid (CSF) pathway and location of cisternal puncture. CSF, secreted by the choroid plexus *(dark blue),* flows through the ventricular system *(medium blue)* from rostral to caudal: lateral ventricles, third ventricle, mesencephalic aqueduct, and fourth ventricle. From there, most of the CSF exits via the lateral apertures of the fourth ventricle and flows cranially and caudally in the subarachnoid space around the brain and spinal cord *(light blue)*. The remainder of CSF flows caudally down the central canal of the spinal cord. CSF from the cranial subarachnoid space enters the venous system via arachnoid villi. Cisternal puncture is performed by placing a needle in the dorsal subarachnoid space at the craniocervical junction. This space usually becomes accessible when the head is ventroflexed.



105.4 INDICATIONS FOR CEREBROSPINAL FLUID COLLECTION AND ANALYSIS

CSF analysis is indicated when a patient has neurologic signs consistent with disease affecting the CNS, including the brain, spinal cord, and nerve roots.[1-3] Advanced imaging (e.g., MRI, computed tomography [CT]) before CSF collection is usually recommended, whenever possible, to help define the underlying neurologic disease.[5] It gives valuable information relating to the exact location of the lesion, the amount and distribution of associated edema, and any structural evidence of intracranial hypertension (ICH). However, regardless of findings on advanced imaging, animals that are showing rapid neurologic deterioration are most likely to benefit from a diagnostic CSF analysis. Common indications for CSF collection in the emergency or critical care setting include the following:

1. Suspected infectious or inflammatory disease affecting the CNS.[6] Conditions causing meningitis, encephalitis, and myelitis are often moderate to severe in nature by the time these animals are showing neurologic signs and CSF analysis should be done as soon as possible. It is always preferable to collect CSF before treating with medications that may influence the content and, subsequently, the interpretation of the findings.
2. Suspected neoplastic disease affecting the CNS.[1,2,6] With the exception of CNS lymphoma, CSF findings alone are rarely specific for neoplastic disease. However, an analysis is often done to rule out the possibility of inflammatory disease that may also be on the differential list, especially if advanced imaging is not available.
3. Animals having cluster or continuous seizures in which underlying infectious or inflammatory disease or neoplasia is likely.[1]
4. Acute, ascending lower motor neuron signs. Because the prognosis and treatment vary widely depending on the underlying cause of these signs, CSF findings may help to differentiate diseases such as acute polyradiculopathy from infectious, inflammatory, or neoplastic disease (e.g., lymphoma).[1]

CSF analysis occasionally may be indicated to monitor short-term response to treatment when an obvious response to therapy is not evident or cannot be monitored. This may be especially applicable to animals that are systemically ill, heavily sedated, or being mechanically ventilated. CSF evaluation, or “the CBC of the CNS,”[1] may be particularly helpful in guiding the clinician in further treatment and prognosis in such cases.

105.5 CONTRAINDICATIONS AND RISKS

CSF collection requires general anesthesia, the risks of which are inherently higher in animals that might have elevated intracranial pressure (ICP).[3,5] Risks of anesthesia are minimized by the following measures:

1. Using an anesthetic protocol that reduces ICP
2. Treating patients with mannitol, ventilation, and control of partial pressure of arterial carbon dioxide before anesthetizing if severe ICH is suspected (see Chapter 100, Intracranial Hypertension)

The emergency clinician should also be aware of the following situations in which the risks of performing a CSF collection are very likely to outweigh benefits, and therefore the procedure is not recommended[1,2]:

- Acute traumatic brain injury
- Rodenticide toxicity, aspirin ingestion, serious coagulopathies
- Severe, progressive ICH

- Atlantoaxial luxation or cranial cervical fracture or luxation

Although CSF analysis is one of the easiest and most direct methods for evaluating the CNS, the proximity of important neural structures makes it possible to penetrate these structures inadvertently during needle placement, especially if there is pathology affecting the subarachnoid space.[1]

The most common injury is trauma to the cerebellum, brainstem, or cervical spinal cord. It produces a vestibular syndrome that is apparent when the animal recovers from anesthesia.[1] A rarer, but more serious, consequence is iatrogenic trauma that produces apnea. Immediate treatment with hyperosmolar therapy, mechanical ventilation, and possibly glucocorticoids, may save the life of the apneic patient.[1] Patients with vestibular signs will usually recover without treatment in a few days to a couple weeks. The incidence of these complications is rare in the hands of a careful, trained individual.

In cases of ICH, herniation of the brain may occur from a rapid reduction of ICP (e.g., pop-off valve effect), producing apnea and unresponsiveness.[1] Usually mydriatic pupils are apparent even while the animal is still anesthetized. Although immediate aggressive treatment for ICH is indicated, these animals have a grave prognosis.

105.6 CEREBROSPINAL FLUID COLLECTION TECHNIQUES

105.6.1 Preparation

For CSF collection and examination it is necessary to puncture the subarachnoid space in the cerebellomedullary cistern or in the lower lumbar spine.[1,3,5,6] Small animals must be anesthetized to ensure complete immobility. A propofol infusion with midazolam or fentanyl, or both, provides excellent anesthesia for performing CSF collection in patients with ICH. The site must be shaved, surgically prepared, and draped with a small fenestrated sterile drape. Sterile surgical gloves should be worn. All equipment should be assembled and ready to use before positioning the patient. The following items are necessary:

1. Sterile gloves and drape or sterile field
2. Disposable spinal needles with stylets

   A 22-gauge, 1½-inch spinal needle is used in most cisternal punctures regardless of size of the dog; it may also be used for cisternal puncture in cats and for lumbar puncture in small dogs and cats.

   A 22-gauge, 2½-inch spinal needle is occasionally necessary for doing a cisternal puncture in giant breed dogs or in large breed dogs with heavy cervical musculature; it is also commonly used in lumbar punctures of most dogs weighing more than 5 kg.

   A 22-gauge, 3½-inch spinal needle is used for lumbar punctures in large and giant breed dogs.

   A 25-gauge, 1-inch spinal needle may be used in small cats and toy breed dogs. These needles are more easily supported by the surrounding tissues in very small animals, and the bevel on the needle is less likely to cause trauma to the brain stem or spinal cord. However, CSF flow is considerably slower through this needle, which should be remembered when watching for the flash of CSF in the hub identifying the subarachnoid space.

3 Red-top glass blood collection tubes (Vacutainers)

105.6.2 Cerebrospinal Fluid Collection Sites and Techniques

CSF collection can be done from the cisterna magna, the lateral ventricle (rarely), or the lumbar region.[1,3,5,6] When focal CNS disease is suspected, CSF findings are more likely to be abnormal and representative of the underlying pathology when they are collected caudal to the lesion. In multifocal or diffuse CNS disease, CSF collection at both cisternal and lumbar sites is recommended.

105.6.2.1 Cisternal Puncture

105.6.2.1.1 Positioning

The subarachnoid space enlarges to form the cerebellomedullary cistern in the dorsal atlantooccipital region (see Figure 105-1).[1,3,5,6] This site is used when the patient's signs suggest brain or cranial cervical spinal cord disease. During cisternal puncture the neck is flexed and a patent airway must be maintained under anesthesia by use of an endotracheal tube. The animal is placed in lateral recumbency (right lateral is usually easiest for a right-handed person) and an area from the occipital protuberance to the level of C3 is surgically prepared.

With the assistant standing opposite the person doing the puncture, the neck is flexed moderately (90 to 100 degrees) at the cisternal region while holding the ears out of the way. It is important to make sure that the midline of the neck and the head (from the nose to the occiput) are perfectly parallel to the tabletop. If the neck sags, as is common in larger dogs, place a small pad under it. Then palpate the wings of the atlas and make sure they are superimposed, eliminating axial rotation. Positioning is critical in making the puncture exactly on midline.

Palpate all landmarks before inserting the needle: external occipital protuberance, spinous process of C2 vertebra, the dorsal arch of C1 vertebra (do this by slipping rostrally off of C2 spine), and the wings of the atlas. Either of the following methods for finding the correct point of insertion may be used:

1. Using the external occipital protuberance and the spine of C2, the puncture is made on midline halfway between the occiput and the cranial end of the spinous process. If the dorsal arch of C1 can be palpated, the puncture is made on the midline just cranial to it.
2. Using the wings of the atlas, the puncture is made in the center of the triangle formed by the occiput and the wings of the atlas.

With either method, a natural indentation can usually be palpated on midline where the needle is most likely to enter the subarachnoid space.

105.6.2.1.2

Needle Insertion

Place the spinal need perpendicular to the plane of the vertebral column and advance it slowly at a 90-degree angle through the skin and underlying tissues. Extremely tough skin, as in cats, may need to be tented and penetrated before the landmarks are identified for puncture into deeper tissues. Every time a layer of tissue is penetrated, detected by a sudden decrease of resistance at the needle tip, remove the stylet and observe the hub of the needle for a few seconds for the appearance of CSF. In small dogs and cats, the tissue planes are not as easily ascertained by feel and the stylet should be removed and checked every 1 to 2 mm. This prevents inadvertent penetration of neural tissue. When the dura is penetrated, resistance decreases and CSF appears in the hub of the needle when the stylet is removed. Occasionally a twitch may be seen or felt when the dura is penetrated, especially if it is inflamed.

105.6.2.2

Tips for Trouble-Shooting Cerebrospinal Fluid Puncture

1. If pure blood drips from the hub, most likely the needle is slightly off midline and into the vertebral venous plexus, outside of the dura. This poses no harm to the patient and the needle should be removed and discarded. Recheck landmarks and patient alignment and try another puncture.

2. If bloody CSF appears in the hub, most likely the needle has traumatically ruptured vessels in the pia. Replace the stylet for a minute, let any blood-tinged CSF flow out, and collect CSF after it clears. CSF that remains uniformly blood tinged may reflect hemorrhage within the CNS. If the tip of the needle is hitting bone, determine if it is hitting C1 or the occipital bone. Pull the needle out slightly and redirect cranially or caudally along the sagittal plane. If bone is encountered repeatedly, it is best to start over with a new needle after rechecking landmarks and patient positioning.

In cats and small dogs, 1 to 2 ml of CSF can be safely collected by free flow into a sterile glass tube; 6 ml or more may be collected in larger dogs.[1-3] It is best not to aspirate fluid from the hub of the needle, because it may collapse the CSF space or initiate hemorrhage.[1] Once enough CSF has been collected, remove the needle. Historically, the opening pressure of the CSF was measured by attaching a stopcock and manometer to the needle before collecting fluid. However, this practice has largely been abandoned for safer, more accurate ways of measuring CSF pressure and is not recommended.[5] If there is concern of life-threatening ICH, it may be safer to attempt a lumbar puncture instead of a cisternal puncture.

PRECAUTION: Especially important in the emergency and critical care setting is to exercise caution when collecting CSF from patients with very high pressures from meningoencephalitis, CNS edema, or an intracranial mass. In these cases it may be dangerous to remove or allow escape of very much CSF. The sudden release of pressure may lead to brain herniation. If CSF flows out of the needle at a high rate, or if flow is initially very good and then suddenly diminishes, a minimal amount of CSF should be collected. Also, in animals with suspected ICH, extreme care should be taken not to severely flex the animal's head or place any compression on jugular veins during CSF collection.

105.6.2.3 Lumbar Puncture

105.6.2.3.1 Positioning

In animals with thoracic, lumbar, or sacral spinal cord disease, CSF should be collected from the lumbar region.[1,6] Additionally, lumbar CSF is usually preferred in animals with ascending lower motor neuron disease or suspected polyradiculopathies. Because of the proximity of the puncture site to the diseased cord and the craniocaudal flow of CSF, lumbar fluid is more likely than cisternal CSF to reflect the disease process. In animals that are too ill to undergo general anesthesia or are comatose, a lumbar puncture (and occasionally a cisternal puncture) can be done with a local anesthetic and a tranquilizer if needed.

The technique of lumbar puncture for collection of CSF is the same as that used to place a needle for injection of contrast material into the subarachnoid space for myelography. CSF analysis should always be done before myelography to rule out meningitis or myelitis, because injecting contrast media when there is inflammation or infection may further damage an injured cord and possibly disseminate infection. If need be, after lumbar spinal needle placement and CSF collection, the patient can be kept under anesthesia with the needle in place for the few minutes needed to do a cell count and differential; then the myelogram can be done if marked inflammation is not present. The patient is positioned in lateral recumbency with the right side down (for a right-handed person). The lumbar spine may be gently flexed to open up the interarcuate space between L4-5 (large breed dogs preferred site), L5-6 (small breed dogs preferred site), or L6-7 (cats preferred site). An area from the midlumbar to the sacral region is clipped and surgically prepped; sterile technique is used as described above.

Palpating the spinous process caudal to the desired interarcuate space, insert the spinal needle through the skin at the caudal lateral edge of the spinous process. With the needle directed cranially and following the spinous process down, insert it until the vertebral arch is encountered. Then "walk" the needle cranially until the interarcuate space is felt. Push the needle gently through the ligament and spinal canal until the floor of spinal canal is encountered. The animal will often twitch when the needle penetrates the dura. If spinal fluid is not seen in the hub of the needle within a few seconds, the needle can be rotated or retracted slowly, or both, until the subarachnoid space is entered and fluid appears. Fluid should be allowed to drip into the collection tube by free flow and not aspirated from the needle. If blood is present in the hub, the needle should be withdrawn and discarded and another puncture attempted at a different site.

NOTE: Although the cauda equina is penetrated in the process of performing the puncture, this usually produces no ill effects.

105.7 ANALYSIS OF CEREBROSPINAL FLUID

Many tests can be done on CSF. To perform all possible tests costs money, requires larger volumes of CSF, and rarely gives additional information except in specific situations. For a complete list of these tests and their normal values, the reader is directed to a clinical pathology textbook or the indicated references at the end of this chapter. The parameters that follow are recommended for routine analysis of CSF samples.

105.7.1 Specimen Handling and Examination

CSF should be collected in sterile red top Vacutainer tubes and analyzed cytologically within 30 to 60 minutes of collection.[1,3,5,6] If it is not possible to evaluate the sample soon after collection, it should be preserved by refrigeration and the addition of 1 drop of fetal calf serum or autologous serum per 0.25 ml of CSF. An aliquot of CSF should be saved in a separate tube for protein measurement. This portion of the sample may be kept refrigerated or frozen until protein analysis is performed. Most commercial laboratories require a total of about 0.5 ml for routine CSF analysis.

105.7.2 Physical Characteristics

The color and clarity of the CSF should be observed by the clinician at the time of collection (Table 105-1).[1-3,6] Normal CSF is a crystal clear, colorless fluid comparable in appearance to that of distilled water. Common abnormalities include cloudiness or turbidity, caused by significant pleocytosis, and xanthochromia, a yellow discoloration caused by the breakdown of RBCs due to recent hemorrhage in the CNS.

Table 105-1 Normal Characteristics of CSF

Characteristic	Findings in Normal CSF
Color	Colorless
Clarity	Transparent, clear
Refractive index	1.3347 to 1.3350
Protein concentration	*Cisternal:* <25 mg/dl
	Lumbar: <40 mg/dl
Total cell count	*RBCs:* 0/µl
	WBCs: <3/µl cisternal; <5/µl lumbar
WBC differential count	Mononuclear cells
	Small mononuclear cells: 60% to 70% Large mononuclear cells: 30% to 40% Polymorphonuclear cells
	Neutrophils: <1%
	Eosinophils: <1% Others
	Ependymal lining cells: rare
	Nucleated RBCs: Rare in lumbar puncture specimens

CSF, Cerebrospinal fluid; *RBC,* red blood cell; *WBC,* white blood cell.

105.7.3 Total Cell Count and Differential

Red and white blood cell (RBC and WBC) counts can be performed in private practice using the chamber of a standard hemacytometer (see Table 105-1).[1,3] One to two drops of CSF are placed on each side of the hemacytometer from a standard microhematocrit tube (without anticoagulant) that has first been coated with new methylene blue stain. The nuclei of the nucleated WBCs in the sample will be stained and readily differentiated from the RBCs. The RBCs and WBCs in the 9 large squares on each side of the hemacytometer are counted. The mean value of the counts from both sides are multiplied by 1.11 to get the total number of cells per cubic millimeter (μl) of spinal fluid.

A differential count is done next, noting polymorphonuclear cells and mononuclear cells. Normal spinal fluid should have fewer than 3 WBCs/μl (slightly higher in lumbar fluid) with no neutrophils, plasma cells, or macrophages. RBCs should not be present in cisternal fluid; however, small numbers are usually considered normal in lumbar fluid. Slight contamination of CSF with blood does not severely affect the counting results.

Higher numbers of RBCs from the peripheral blood may affect the total WBC count, and the following rule of thumb is often used to make a “ballpark” correction estimate. Because the normal ratio of red cells to white cells in blood is about 500:1, 1 WBC is subtracted from the total CSF WBC count for every 500 RBCs present in the CSF, if the patient's peripheral blood count is in the normal range. For more in-depth explanation on interpreting blood contaminated CSF, the reader is referred to the reference list.

105.7.4 Cytology

Most CSF samples contain low numbers of WBCs, and therefore most samples will need to be concentrated before microscopically examining morphology (see Table 105-1).[1,3] Commercial labs use a cytocentrifuge to concentrate the cells in a single drop of CSF on a microscope slide. Membrane filtration and sedimentation are 451 alternative methods of 452 cytologic analysis. In-house sedimentation chambers can be constructed easily and used in private practice (see reference list). The slides made using a sedimentation chamber may be examined in-house or submitted to a commercial laboratory for morphologic evaluation.

105.7.5 Protein

Total protein may be measured by several methods, although quantitative protein determinations performed by commercial laboratories are the most accurate (see Table 105-1).[1,3,5,6] Normal values vary among species, laboratories, and site of collection. Most diseases of the CNS will cause changes in the CSF protein concentration; elevated protein concentration in the CSF often is used as evidence that neurologic disease is within the CNS. The degree of protein elevation is used, along with information on the total and differential WBC count, to determine the most likely differential(s) for the abnormalities seen in the sample. Blood contamination of the CSF (>500 RBC/μl) may influence protein concentration and should be taken into account. A 1 mg/dl increase in CSF protein can be estimated for every 1000 RBCs in the sample if the serum protein concentration of the patient is in the normal range. For more in-depth discussions on protein concentration and interpretation, see the reference section.

105.7.6 Other Tests

Many other diagnostic tests may be done on CSF samples depending on the interpretation of the cytology findings and protein concentration. These include bacterial culture, antigen-antibody titers, polymerase chain reaction (PCR), immunocytochemistry, and enzyme, metabolite, and neurotransmitter assays.[1,6]

105.8 INTERPRETATION OF COMMON FINDINGS

Although CSF results are usually not specifically diagnostic, certain types of cellular responses can be strongly suggestive of particular diseases.[1-3,5,6] There are many exceptions to the general guidelines presented below, especially when adding the complexity of evaluating CSF from animals that have chronic disease or have been treated with medications that may affect the cellular content or distribution of cells. It must also be kept in mind that normal CSF findings do not rule out the presence of CNS disease.

1 Mild to moderate predominantly mononuclear pleocytosis typically is seen with inflammatory diseases, especially viral and rickettsial infections (e.g., canine distemper, ehrlichia). It may also occur with noninfectious inflammatory brain diseases as well as compressive lesions affecting the spinal cord (intervertebral disk disease [IVDD]).

2 Moderate to marked predominantly neutrophilic pleocytosis most commonly is seen with infectious or inflammatory diseases such as bacterial meningoencephalomyelitis, steroid-responsive meningitis or vasculitis, and feline infectious peritonitis.

3 Moderate to marked predominantly mononuclear pleocytosis classically is seen with granulomatous meningoencephalomyelitis and breed-related forms of necrotizing encephalitis seen in Pugs, Maltese, Yorkshire Terriers, Chihuahuas, and others. Lymphoma in the CNS often causes significant mononuclear pleocytosis as well.

4 Marked pleocytosis with a predominance of eosinophils most commonly is caused by eosinophilic meningitis (idiopathic). Other less common conditions, such as parasitic migrations (e.g., *Angiostrongylus*) and protozoal and fungal disease, should also be considered.

5 Mild to marked mixed pleocytosis most often is associated with inflammatory diseases, especially fungal or protozoal meningoencephalomyelitis. Mixed pleocytoses are also commonly seen in infectious or inflammatory disease that is “aging” or being managed with medications that are altering the typical pattern of cells seen. Necrosis of the CNS occurring secondary to vascular infarction, trauma, or neoplasia may also produce a mixed pleocytosis.

6 Albuminocytologic dissociation occurs when the total nucleated cell count is in the normal range (although the distribution of cells may be abnormal) but the protein is elevated. This finding is very nonspecific and may be seen with virtually any CNS disease, but it is most often indicative of degenerative or demyelinating diseases (degenerative myelopathy), chronically compressive lesions (IVDD, neoplasia, stenoses), and intramedullary pathology (neoplasia or syringohydromyelia).

105.9 SUGGESTED FURTHER READING*

RS Bagley: Treatment of important and common diseases involving the intracranial nervous system of dogs and cats. In RS Bagley (Ed.): *Fundamentals of veterinary clinical neurology*. ed 1, 2005, Blackwell, Ames, IA, *Concise, easy-to-read explanations of CSF interpretation.*

CS Bailey, W Vernau: Cerebrospinal fluid. In JJ Kaneko, JW Harvey, ML Bruss (Eds.): *Clinical biochemistry of domestic animals*. ed 5, 1997, Academic Press, San Diego, *An excellent detailed, yet concise, chapter incorporating all the current information on CSF physiology and interpretation in dogs and cats*.

CL Chrisman: Cerebrospinal fluid analysis. In MP Moore (Ed.): *Veterinary Clinics of North America: diseases of the spine*. **vol 22**, 1992, Saunders, Philadelphia, no 4 *A good summary reference article on CSF in small animals*.

RA Fishman: In *Cerebrospinal fluid in diseases of the nervous system*. ed 2, 1992, Saunders, Philadelphia, *The CSF "bible" containing in-depth information on most aspects of CSF physiology and interpretation*.

A Tipold: Cerebrospinal fluid. KG Braund (Ed.): In *Braund's clinical neurology in animals: localization, diagnosis, and treatment*. 2005, International Veterinary Information Service, Philadelphia, *A useful reference reviewing both techniques for CSF sampling and analysis*.

H Wamsley, RA Alleman: Clinical pathology. In NJ Olby, SR Platt (Eds.): *BSAVA manual of canine and feline neurology*. 2000, British Small Animal Veterinary Association, Gloucester, England, *Contains helpful illustrations and a useful description on setting up an in-house sedimentation chamber*.

* See the CD-ROM for a complete list of references

54 Chapter 54 Sodium Disorders

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54.1 KEY POINTS

- Most disorders of plasma sodium concentration result from abnormalities in the handling of water rather than sodium.
- Plasma sodium concentration is the major determinant of plasma osmolality.
- Hypernatremia or hyponatremia can cause central nervous system (CNS) disturbance resulting from changes in neuronal cell volume and function.
- Overly rapid correction of hypernatremia or hyponatremia can cause severe CNS dysfunction.
- Patients with hypernatremia or hyponatremia that require intravascular volume expansion should be treated with intravenous fluids that match their plasma sodium concentration.

54.2 INTRODUCTION

Sodium concentration is expressed as milliequivalents (mEq) of sodium per liter of serum or plasma. In the vast majority of cases, disorders of sodium concentration in dogs and cats result from abnormalities in water handling rather than an increased or decreased number of sodium molecules. To understand what determines plasma sodium concentration and how changes in plasma sodium concentration alter cellular function, one must understand the distribution of body water and the concept and determinants of osmolality.

54.2.1 Distribution of Total Body Water

Water makes up approximately 60% of an adult animal's body weight; two thirds is intracellular and one third is extracellular. Extracellular water is distributed between the interstitial and intravascular compartments, which contain approximately 75% and 25% of the extracellular water, respectively (see Figure 64-1). The endothelium, which separates the intravascular fluid compartment from the interstitial space, and the cell membrane, which separates the interstitial and intracellular compartments, are freely permeable to water molecules. Therefore, in a closed system (no urinary or gastrointestinal (GI) output), when 1 L of free water (water containing no other molecules) is added to the animal, 666 ml will be distributed to the intracellular space and 333 ml to the extracellular space. Of the 333 ml added to the extracellular space, 250 ml will remain in the interstitial fluid space and 83 ml will be distributed to the intravascular compartment.

54.2.2 Osmolality and Osmotic Pressure

An *osmole* is one mole of any fully dissociated substance dissolved in water. *Osmolality* is the concentration of osmoles in a mass of solvent. In biologic systems, osmolality is expressed as mOsm/kg of water. *Osmolarity* is the concentration of osmoles in a volume of solvent, and in biologic systems is expressed as mOsm/L of water. Every molecule dissolved in the total body water contributes to osmolality, regardless of size, weight, charge, or composition. The most abundant osmoles in the extracellular fluid are sodium and potassium (and their accompanying anions chloride and bicarbonate), glucose, and urea. Hence, these molecules are the main determinants of plasma osmolality in healthy dogs and cats.

Plasma osmolality in healthy animals is approximated by the equation:

$2(\mathrm{Na}^{+} + \mathrm{K}^{+}) + (\mathrm{BUN}\,[\mathrm{mg} / \mathrm{dl}] \div 2.8) + (\mathrm{glucose}\,[\mathrm{mg} / \mathrm{dl}] \div 18)$ where Na^{+} = sodium, K^{+} = potassium, and BUN = blood urea nitrogen.

The blood urea nitrogen (BUN) and glucose concentrations are divided by 2.8 and 18, respectively, to convert them to mOsm/kg. As this equation shows, plasma sodium concentration is the major determinant of plasma osmolality.

Osmoles that do not cross the cell membrane freely are considered *effective osmoles,* whereas those that do cross freely are termed *ineffective osmoles*. The water-permeable cell membrane is functionally impermeable to sodium and potassium. As a result, sodium and potassium molecules are effective osmoles and they exert osmotic pressure across the cell membrane. The net movement of water into or out of cells is dictated by the osmotic pressure gradient. Osmotic pressure causes water molecules from an area of lower osmolality to move to an area of higher osmolality until the osmolalities of the compartments are equal.

When sodium is added to the extracellular space at a concentration greater than that in the extracellular fluid, intracellular volume decreases (the cell shrinks) as water leaves the cell along its osmotic pressure gradient. Conversely, cells swell when free water is added to the interstitial space and water moves intracellularly along its osmotic pressure gradient.

54.2.3 Regulation of Plasma Osmolality

Hypothalamic osmoreceptors sense changes in plasma osmolality, and changes of only 2 to 3 mOsm/kg induce compensatory mechanisms to return the plasma osmolality to its hypothalamic setpoint.[1] The two major physiologic mechanisms for controlling plasma osmolality are the antidiuretic hormone (ADH) system and thirst.

54.2.3.1 Antidiuretic Hormone

ADH is a small peptide secreted by the posterior pituitary gland. There are two major stimuli for ADH release: 224
elevated plasma osmolality and decreased effective circulating volume. Increased plasma osmolality causes 225
shrinkage of a specialized group of cells in the hypothalamus called *osmoreceptors*. When their cell volume decreases, these hypothalamic osmoreceptors send impulses via neural afferents to the posterior pituitary, leading to ADH release.[2] When effective circulating volume is low, baroreceptor cells in the aortic arch and carotid bodies send neural impulses to the pituitary gland that stimulate ADH release.

In the absence of ADH, renal tubular collecting cells are relatively impermeable to water. When ADH activates the V_2 receptor on the renal collecting tubular cell, aquaporin-2 molecules are inserted into the cell's luminal membrane. Aquaporins are channels that allow the movement of water into the renal tubular cell. Water molecules cross through these aquaporins into the hyperosmolar renal medulla down their osmotic gradient. If the kidney is unable to generate a hyperosmolar renal medulla because of disease or diuretic administration, water will not be reabsorbed, even with high concentrations of ADH. Thus, circulating ADH concentration and ADH's effect on the normal kidney are the primary physiologic determinants of free water retention and excretion.

54.2.3.2 Thirst

Hyperosmolality and decreased effective circulating volume also stimulate thirst. The mechanisms by which hyperosmolality and hypovolemia stimulate thirst are similar to those that stimulate ADH release. Thirst and the resultant water consumption are the main physiologic determinants of free water intake.

54.2.4 Prioritization of Osmolality and Effective Circulating Volume

Under normal physiologic conditions, the renin-angiotensin-aldosterone system monitors and fine tunes effective circulating volume, and the ADH system maintains normal plasma osmolality. However, maintenance of effective circulating volume is always prioritized over maintenance of normal plasma osmolality. Therefore patients with poor effective circulating volume will have increased thirst and ADH release regardless of their osmolality. The resultant increased free water intake (from drinking) and water retention (from ADH action at the level of the kidney) can lead to hypoosmolality in patients with poor effective circulating volume. An example of the defense of effective circulating volume at the expense of normal plasma osmolality is seen in patients with chronic congestive heart failure that present with hyponatremia.[3]

54.2.5 Total Body Sodium Content Versus Plasma Sodium Concentration

Plasma sodium concentration is different than, and independent of, total body sodium content. Total body sodium content refers to the total number of sodium molecules in the body, regardless of the ratio of sodium to water. Sodium content determines the *hydration status* of the animal. As it is used clinically, *hydration* is a misnomer, because findings such as skin tenting and moistness of the mucous membranes and conjunctival sac are determined by the sodium content and the water that those sodium molecules hold in an animal's interstitial space.

When patients have increased total body sodium, an increased quantity of fluid is held within the interstitial space and the animal appears overhydrated, regardless of the plasma sodium concentration. Overhydrated patients may manifest a gelatinous subcutis, peripheral, or ventral pitting edema, chemosis, or excessive serous nasal discharge.

When patients have decreased total body sodium, a decreased quantity of fluid is held within the interstitial space and the animal appears dehydrated, regardless of the plasma sodium concentration. Once a patient has lost 5% or more of its body weight in isotonic fluid (≥5% dehydrated), it may manifest decreased skin turgor, tacky or dry mucous membranes, decreased fluid in the conjunctival sac, or sunken eye position. Patients that are less than 5% dehydrated appear clinically normal. Patients with dehydration can become hypovolemic as fluid shifts from the intravascular space into the interstitial space as a result of decreased interstitial hydrostatic pressure.

The sodium-to-water ratio is independent of the total body sodium content: patients may be normally hydrated, dehydrated, or overhydrated (normal, decreased, or increased total body sodium content) and have a normal plasma sodium concentration, hypernatremia, or hyponatremia.

54.3 HYPERNATREMIA

Hypernatremia is defined as plasma or serum sodium concentration above the reference interval. Hypernatremia is common in critically ill dogs and cats.

54.3.1

Etiology

Most dogs and cats with hypernatremia have increased free water loss rather than increased sodium intake or retention.

54.3.1.1

Free Water Deficit

Normal animals can become severely hypernatremic if denied access to water for extended periods. Animals with vomiting, diarrhea, or polyuria of low-sodium fluid may also develop hypernatremia. Diabetes insipidus (DI), a syndrome of inadequate release of or response to ADH, can cause hypernatremia (see Chapter 70, Diabetes Insipidus). Animals with DI become severely hypernatremic when they do not drink water, because they cannot reabsorb free water in the renal collecting duct. Acute or critical illness can unmask previously undiagnosed DI.[4] A syndrome of hypodipsic hypernatremia has been reported in Miniature Schnauzers,[5-7] one of which was diagnosed with congenital holoprosencephaly.[5] This syndrome is most likely due to impaired osmoreceptor or thirst center function. In other dog breeds and cats, hypodipsic hypernatremia has been associated with hypothalamic granulomatous meningoencephalitis, hydrocephalus, and other central nervous system (CNS) deformities and CNS lymphoma.[8-12]

Diagnostic differentiation between central DI, nephrogenic DI, and hypodipsic hypernatremia can be complex and is outside the scope of this chapter. The reader is referred to more detailed texts for further information.[13-15]

54.3.1.2

Sodium Excess

Severe hypernatremia can also occur with the introduction of large quantities of sodium in the form of sodium bicarbonate, sodium phosphate enemas,[16] seawater, beef jerky, and salt-flour dough mixtures.[17]

54.3.2

Clinical Signs

Hypernatremia causes no specific clinical signs in many cases. If it is severe (usually >180 mEq/L) or occurs rapidly, it may be associated with CNS signs such as obtundation, head pressing, seizures, coma, and death. All cells that have Na^+/K^+-ATPase pumps shrink as a result of hypernatremia as water moves out of the cell down its osmotic gradient to the relatively hyperosmolar extracellular compartment, but those of the CNS are clinically the least tolerant of this change in cell volume.

An experimental study found decreased myocardial contractility during injection of hypernatremic or hyperosmolar solutions in dogs.[18] Hypernatremia has also been associated with hyperlipidemia, possibly a result of the inhibition of lipoprotein lipase.[10] Artifactual hemogram changes in the blood of two hypernatremic cats have been reported with a specific hematology analyzer.[19]

54.3.3

Physiologic Adaptation to Hypernatremia

Hypernatremia causes free water to move out of the relatively hypoosmolar intracellular space into the hyperosmolar extracellular space, leading to decreased cell volume. When the cell shrinks, intracellular mechanisms sense the decreased cell volume and build *idiogenic osmoles,* or *osmolytes,* such as inositol to increase intracellular osmolality, which causes water to move back into the cell and restores cell volume to normal. Generation of these idiogenic osmoles begins within a few hours of cell shrinkage, but full compensation takes approximately 24 hours. This restoration of intracellular volume is important for cellular function and is an important consideration during treatment of hypernatremia, as discussed later.

54.3.4 Treatment of the Normovolemic, Hypernatremic Patient

Hypernatremia should be treated, even if no clinical signs are apparent. Patients with hypernatremia have a free water deficit, so free water is replaced in the form of fluid with a lower effective osmolality than that of the patient. Treatment must be cautious, and close monitoring of plasma or serum sodium concentration and CNS signs is imperative.

In patients with mild to moderate hypernatremia ($[Na^+]_p$ <180 mEq/L), sodium concentration should be decreased at a rate of 1 mEq/L/hr. In those with severe hypernatremia ($[Na^+]_p$ ≥180 mEq/L), it should be decreased at a maximum rate of 0.5 to 1 mEq/L/hr. This slow decrease in plasma sodium concentration ($[Na^+]_p$) is important to prevent cellular swelling. Idiogenic osmoles are broken down slowly, so rapid drops in plasma sodium concentration (and thus plasma osmolality) cause free water to move back into the relatively hyperosmolar intracellular space and can lead to neuronal edema.

Free water deficit can be calculated by the formula:

$$\text{Free water deficit} = ([\,\text{current}\,[\text{Na}^+]_p \div \text{normal}\,[\text{Na}^+]_p\,] - 1) \times (0.6 \times \text{body weight in kg})^2$$

This formula gives the total volume of free water that needs to be replaced. This volume of free water, usually 5% dextrose in water, is infused over the number of hours calculated for safe reestablishment of normal plasma sodium concentration. This rate of free water replacement may be inadequate in cases of ongoing free water loss, as seen with diuresis of electrolyte-free water in patients with DI or unregulated diabetes mellitus, but it is a safe starting point in most cases.

Plasma sodium concentration should be monitored no less frequently than every 4 hours to assess the adequacy of treatment, and CNS status should be monitored continuously for signs of obtundation, seizures, or other abnormalities. The rate of free water supplementation should be adjusted as needed to ensure an appropriate drop in plasma sodium concentration, the goal being a drop of no more than 1 mEq/hr and no signs of cerebral edema. Water may be supplemented intravenously (as 5% dextrose in water) or orally on an hourly schedule in animals that are alert, willing to drink, and not vomiting. It is important to note that free water replacement alone will not correct clinical dehydration or hypovolemia, because free water replacement does not provide the sodium required to correct these problems (see Total Body Sodium Content Versus Plasma Sodium Concentration). Free water replacement in the hypernatremic patient is relatively safe, even in animals with cardiac or renal disease, because two thirds of the volume administered will enter the cells.

54.3.5 Complications of Therapy for Hypernatremia

Cerebral edema is the primary complication of therapy for hypernatremia. Clinical signs of cerebral edema include obtundation, head pressing, coma, seizures, and other disorders of behavior or movement. If these signs develop during the treatment of hypernatremia, immediately stop the administration of any fluid that has a lower sodium concentration than the patient and disallow drinking. The patient's plasma sodium concentration should be measured to confirm that it is lower than it was when treatment was instituted. This is an important step, because signs of worsening hypernatremia may be similar to those seen with cerebral edema. If the plasma sodium concentration has decreased, even if it has dropped at less than 1 mEq/L/hr, cerebral edema should be considered.

Cerebral edema is treated with a slow, single bolus dose of mannitol at 0.5 to 1 g/kg IV over 20 to 30 minutes. Mannitol should be administered via a central vein if possible, but it may be diluted 1:1 in sterile water and given through a peripheral vein in an emergency situation. If mannitol is not available, or if a single dose does not improve signs, consider a dose of 7.2% Na^+ sodium chloride at 3 to 5 ml/kg over 20 minutes. The administration method is similar to that used for mannitol. Do not administer hypertonic saline as a rapid bolus, because it can cause vasodilation.

54.4 HYPONATREMIA

Hyponatremia is defined as plasma or serum sodium concentration below the reference interval. Clinically relevant hyponatremia is uncommon in critically ill dogs and cats.

54.4.1 Etiology

Dogs and cats with hyponatremia almost always have free water retention in excess of total body sodium. Generation of hyponatremia usually requires water intake in addition to impaired water excretion.

54.4.1.1 Decreased Effective Circulating Volume

A common cause of hyponatremia in dogs and cats is decreased effective circulating volume, which causes ADH release and water intake in defense of intravascular volume, and thus decreases plasma sodium concentration. Possible causes include congestive heart failure,[3] excessive gastrointestinal losses,[20,21] excessive urinary losses, body cavity effusions,[22,23] and edematous states. Note that in the case of congestive heart failure, the patient has increased total body sodium (is “overhydrated”) because of activation of the renin-angiotensin-aldosterone system, yet is hyponatremic due to increased water retention in excess of sodium retention. In the case of excessive salt and water losses from the GI or urinary tract, the patient is total body sodium depleted (is “dehydrated”) and is hyponatremic due to compensatory water drinking and retention to maintain effective circulating volume.

54.4.1.2 Hypoadrenocorticism

Hypoadrenocorticism leads to hyponatremia through decreased sodium retention (due to hypoaldosteronism) combined with increased water drinking and retention in defense of inadequate circulating volume. Animals with atypical hypoadrenocorticism, whose aldosterone production and release are normal, may also develop hyponatremia, because low circulating cortisol concentration leads to increased ADH release and resultant water retention regardless of intravascular volume status.[24]

54.4.1.3 Diuretics

Thiazide or loop diuretic administration can lead to hyponatremia by induction of hypovolemia, hypokalemia that causes an intracellular shift of sodium in exchange for potassium, and the inability to dilute urine.[24] Renal failure can cause hyponatremia by similar mechanisms.

54.4.1.4 Syndrome of Inappropriate Antidiuretic Hormone Secretion

Syndrome of inappropriate ADH secretion (SIADH) causes hyponatremia through water retention in response to improperly high circulating concentrations of ADH. The syndrome has been reported in dogs[25,26] and has many known causes in humans[24] (see Chapter 71, Syndrome of Inappropriate Antidiuretic Hormone).

54.4.1.5 Other Causes of Hyponatremia

Hyponatremia has been reported in animals with GI parasitism,[21] other infectious diseases,[27,28] psychogenic polydipsia, and pregnant dogs.[29] A syndrome of cerebral salt wasting has been described in humans with CNS disease but has not been reported clinically in dogs or cats. Cerebral salt wasting is differentiated from SIADH by evaluation of hydration status: patients with cerebral salt wasting are clinically dehydrated because of a decrease in total body sodium content, and those with SIADH are usually adequately hydrated with excessive free water retention.[30]

54.4.2 Clinical Signs

Mild to moderate hyponatremia usually causes no specific clinical signs. If hyponatremia is severe (usually <120 mEq/L) or occurs rapidly, it may be associated with CNS signs such as obtundation, head pressing, seizures, coma, and death. All cells that have Na^+/K^+-ATPase pumps swell as a result of hyponatremia as water moves into the relatively hyperosmolar cell from the hypoosmolar extracellular space, but those of the CNS are clinically the least tolerant of this change in cell volume.

An experimental study found increased myocardial contractility during injection of hyponatremic or hypoosmolar solutions in dogs.[18] Hyponatremia decreases renal concentrating ability in dogs.[31] There is one report of artifactual hemogram changes in canine blood secondary to hyponatremia using a specific hematology analyzer.[19]

54.4.3 Physiologic Adaptation to Hyponatremia

Hyponatremia causes free water to move into the relatively hyperosmolar cell from the hypoosmolar extracellular space, leading to increased cell volume. Interstitial and intracellular CNS edema increases intracranial tissue hydrostatic pressure. This pressure enhances fluid movement into the cerebrospinal fluid, which flows out of the cranium, through the subarachnoid space and central canal of the spinal cord, and back into venous circulation. Swollen neurons also expel solutes such as sodium, potassium, and organic osmolytes to decrease intracellular osmolality and encourage water loss to the ECF, returning cell volume toward normal. Ion expulsion occurs rapidly, but loss of organic osmolytes requires hours to days. Therefore clinical signs associated with hyponatremia, and potential complications of management, are associated with both the magnitude and rate of sodium concentration change.

54.4.4 Treatment of the Normovolemic, Hyponatremic Patient

The general goal in the treatment of hyponatremia is to raise plasma sodium concentration slowly toward the lower end of the reference interval, at a rate no greater than 0.5 to 1 mEq/L per hour. The exception is in cases of symptomatic or severe hyponatremia ($[Na^+]_p$ <120 mEq/L), when a rapid increase of plasma sodium to 120 mEq/L is desirable.

Hyponatremia due to decreased effective circulating volume is most often mild ($[Na^+]_p \geq 130$ mEq/L) and usually self-corrects with appropriate treatment of the underlying disease. Fluids with a sodium concentration less than that of the patient should be avoided. The plasma sodium concentration and the patient's CNS status should be monitored regularly, but complications of hyponatremia or its treatment are unlikely to occur in these situations. Patients with hyponatremia due to congestive heart failure will likely remain hyponatremic as a result of diuretic administration, the resultant polydipsia, and ingestion of a low-sodium diet.

Patients with moderate to severe hyponatremia ($[Na^+]_p$ <130 mEq/L), or with CNS signs due to hyponatremia, 227

228 should be managed carefully. Asymptomatic patients that are edematous may be treated with water restriction alone, and those that are asymptomatic and normally hydrated or dehydrated may be treated with administration of fluids containing a higher sodium concentration than that of the patient.

In the emergency situation of symptomatic hyponatremia, when plasma sodium concentration is less than 120 mEq/L, or in cases in which conservative treatment is ineffective, therapy is more aggressive. The most reliable method for ensuring excretion of free water is administration of mannitol (0.5 to 1 g/kg IV over 20 to 30 minutes) along with furosemide (0.5 to 1 mg/kg IV) to ensure that electrolyte-free water is excreted along with the mannitol. Fluid loss should be replaced with standard replacement intravenous fluids, unless the patient is overhydrated and the fluid loss desired. Further explanation of this technique is available for review elsewhere.[32] The goal is to raise the plasma sodium concentration by no more than 10 mEq/L during the first 24 hours, and by no more than 18 mEq/L during the first 48 hours of treatment, never to exceed the low end of the reference interval. The limit of 10 mEq/L during the first day of treatment is more important than the rate over a specific period within that day.[24] It seems reasonable to be even more cautious in asymptomatic patients to minimize the likelihood of complications.

54.4.5 Complications of Therapy for Hyponatremia

The major complication of treatment for hyponatremia is myelinolysis. Myelinolysis is a result of neuronal shrinking away from the myelin sheath as water moves out of the neuron during correction of hyponatremia. Clinical signs of myelinolysis usually manifest many days after intervention, so the clinician cannot assume that a rapid change in plasma sodium concentration has been well tolerated simply because no CNS signs are present during initial treatment. Overzealous correction of severe hyponatremia has led to paresis, ataxia, dysphagia, obtundation, and other neurologic signs in dogs.[33-36] All of these dogs had initial plasma sodium concentrations of less than 110 mEq/L, and all had sodium concentration corrections that exceeded the above- recommended rate. Myelinolysis lesions in dogs are commonly seen in the thalamus, rather than the pons as in humans. Patients with myelinolysis may recover with intensive supportive treatment, although some do not.

Because the signs of myelinolysis are delayed, it is rare for a patient to develop abnormal CNS signs during initial treatment of hyponatremia. However, if new neurologic signs develop during treatment, administration of any fluid that is hyperosmolar to the patient (mannitol, hypertonic or isotonic fluids) should be stopped. The patient's plasma sodium concentration is checked to confirm that it has increased. This is an important step, because signs of worsening hyponatremia may be similar to those seen with treatment. If the plasma sodium concentration is higher than it was at the initiation of treatment, even if the concentration has increased slowly, CNS damage should be considered. Treatment of CNS signs due to overly rapid correction of hyponatremia requires administration of free water to drop the plasma sodium concentration by 1 mEq/L. Decreasing sodium concentration in an already hyponatremic animal can be difficult unless the patient is treated with a loop diuretic such as furosemide to clamp urine osmolality, and water is replaced simultaneously.

54.5 PSEUDOHYPONATREMIA

Pseudohyponatremia is the term used to describe hyponatremia in a patient with normal or elevated plasma osmolality. The most common cause of pseudohyponatremia in dogs and cats is hyperglycemia. Glucose is an effective osmole, so when hyperglycemia is present, the excess glucose molecules cause an increase in ECF water, diluting sodium to a lower concentration. For each 100 mg/dl increase in blood glucose, sodium concentration drops by approximately 1.6 mEq/L.[24] This effect is nonlinear, however; mild hyperglycemia leads to smaller changes in plasma sodium concentration than more severe hyperglycemia (see Chapter 68, Hyperglycemic Hyperosmolar Syndrome, for more information about this condition in diabetes mellitus). Pseudohyponatremia does not require specific treatment, and the sodium concentration will increase as the hyperglycemia resolves and water moves back into the cells. The other common cause of pseudohyponatremia in dogs and cats is mannitol infusion with retention (rather than renal excretion) of mannitol molecules.

54.6 VOLUME EXPANSION IN THE HYPOVOLEMIC, HYPONATREMIC, OR HYPERNATREMIC PATIENT

Patients with moderate to severe abnormalities in sodium concentration ($[Na^+]_p$ <130 or >170) that require intravascular volume expansion should be resuscitated with a fluid that has a sodium concentration that matches that of the patient (± 6 mEq/L). Hyponatremic animals may be resuscitated with a balanced electrolyte solution containing 130 mEq/L sodium if appropriate, or with a maintenance solution that has sodium chloride added to bring the sodium concentration of the solution up to that of the patient. Hypernatremic animals should be resuscitated with a balanced electrolyte solution with NaCl added in a quantity sufficient to bring the solution's sodium concentration up to that of the animal. The simplest way to add sodium to a bag of commercially available fluid is to add 23.4% NaCl to the bag. This product contains 4 mEq NaCl per ml of solution, so it adds a significant quantity of sodium in a small volume.

54.7 SUGGESTED FURTHER READING*

G Giebisch, E Windhager: Integration of salt and water balance. In WF Boron, EL Boulpaep (Eds.): *Medical physiology*. 2003, Saunders, Philadelphia, *Chapter that provides an excellent overview of both the normal physiology and the pathophysiology of sodium and water handling. Thorough explanations in an easy-to-read format with excellent figures to enhance understanding.*

BF Palmer: Hyponatremia in patients with central nervous system disease: SIADH versus CSW. *Trends Endocrinol Metab*. **14**, 2003, 182, *Article that provides an outstanding review of the basic pathophysiology of*

SIADH and cerebral salt wasting, and includes instructions for differentiating the two syndromes in hyponatremic patients.

P Porzio, M Halberthal, D Bohn, et al.: Treatment of acute hyponatremia: ensuring the excretion of a predictable amount of electrolyte-free water. *Crit Care Med*. **28**, 2000, 1905, *Recounting of a case of deleterious hyponatremia in a human patient, providing an excellent review of ideal treatment. Article that explains in detail the mechanism of free water excretion seen when mannitol and furosemide are used in conjunction in the hyponatremic patient. Helpful figures and tables included.* 228

229 BD Rose, TW Post: Hyperosmolal states: hypernatremia. In BD Rose, TW Post, B Rose (Eds.): *Clinical physiology of acid–base and electrolyte disorders*. ed 5, 2001, McGraw-Hill, New York, *Chapter on hyperosmolal states that is extensive in its review of pathophysiology, causes, sequelae, and treatment of hyperosmolal states in humans.*

BD Rose, TW Post: Hypoosmolal states: hyponatremia. In BD Rose, TW Post, B Rose (Eds.): *Clinical physiology of acid-base and electrolyte disorders*. ed 5, 2001, McGraw-Hill, New York, *Chapter on hypoosmolal states that is extensive in its review of pathophysiology, causes, sequelae, and treatment of hyponatremia and hypoosmolal states in humans.*

* See the CD-ROM for a complete list of references

55 Chapter 55 Potassium Disorders

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55.1 KEY POINTS

- Normal serum potassium concentration is essential for normal neuromuscular function.
- Common predisposing conditions for potassium abnormalities include diabetes mellitus, chronic renal disease (especially in cats), and metabolic alkalosis.
- The main clinical manifestation in the dog and cat is hypokalemic myopathy.
- Rate of potassium infusion rather than total amount infused is of major therapeutic importance.
- Mild to moderate hypokalemia (serum potassium 2.5 to 3.5 mEq/L) can be corrected at a rate up to 0.5 mEq/kg per hour.
- Decreased renal excretion is the most common cause of hyperkalemia in small animal patients.
- Before determination of serum potassium level in any hyperkalemic patient or in any animal with urinary tract obstruction, an electrocardiogram (ECG) should be evaluated to detect bradycardia, atrial standstill, or ventricular arrhythmias.
- Renal failure, hypoadrenocorticism, and gastrointestinal disease are the most common causes of sodium-to-potassium ratios less than 27:1.
- When serum potassium exceeds 8 mEq/L or severe ECG changes are present, immediate therapy directed toward reducing and antagonizing serum potassium is warranted (i.e., 10% calcium gluconate, sodium bicarbonate, dextrose with or without insulin).

55.2 INTRODUCTION

Few of the disturbances in fluid and electrolyte metabolism are as frequently encountered or as immediately life threatening as disturbances in potassium balance. Many clinicians are already sensitized to the detrimental effects of potassium disorders, especially hyperkalemia, but sometimes the adverse effects of hypokalemia are nearly as harmful. This chapter will discuss the clinical essentials of hypokalemia and hyperkalemia in the dog and cat and show why both are important to patient care.

55.2.1 Normal Distribution of Potassium in the Body

Potassium is the most abundant intracellular cation, with 98% to 99% located in the intracellular compartment. Most intracellular potassium lies in the skeletal muscle cells. The average potassium concentration in the intracellular space of dogs and cats is 140 mEq/L, and that in the plasma space averages 4 mEq/L.[1,2] Serum potassium levels therefore do not reflect tissue concentrations.

55.3 HYPOKALEMIA

55.3.1 Definition and Causes

Hypokalemia occurs when the serum potassium concentration is less than 3.5 mEq/L (normal range 3.5 to 5.5 mEq/L). The general causes of hypokalemia are: (1) disorders of internal balance and (2) disorders of external balance. The clinical conditions most commonly associated with each of these are provided in Box 55-1.

55.3.2 Consequences

Abnormalities resulting from hypokalemia are divided into four categories: metabolic, neuromuscular, renal, and cardiovascular. Glucose intolerance is the most notable adverse metabolic effect of hypokalemia. Experiments have shown that release of insulin from the pancreatic β-cells is impaired when total body potassium levels are decreased.[10]

Potassium is necessary for maintenance of normal resting membrane potential. Subsequently, the most significant neuromuscular abnormality induced by hypokalemia in dogs and cats is skeletal muscle weakness from hyperpolarized (less excitable) myocyte plasma membranes that may progress to hypopolarized membranes.[9-12] Ventroflexion of the head and neck, a stiff, stilted gait, and a plantigrade stance may also be evident. In cats, hypokalemic myopathy typically is associated with chronic renal disease and poorly regulated diabetes mellitus.[2,13] It can also result from a potassium-deficient diet.[13] Frank paralysis and death due to diaphragmatic failure and respiratory muscle failure can occur in severe cases. Hypokalemia can also cause rhabdomyolysis, which may have a toxic effect on the renal tubules.[9,11] Smooth muscle impairment can also occur, leaving the patient with paralytic ileus and gastric atony.[7] These neuromuscular signs are seldom present until serum potassium levels fall below 2.5 mEq/L. Cats with chronic renal disease can become markedly potassium depleted, and the resulting hypokalemia can impair renal tubular function.[2,13,14]

In the myocardial cell, a high intracellular-to-extracellular potassium concentration ratio induces a state of electrical hyperpolarization leading to prolongation of the action potential. This may predispose the patient to atrial and ventricular tachyarrhythmias, atrioventricular dissociation, and ventricular fibrillation. Abnormal ECG findings in animals with hypokalemia are less reliable than in those with hyperkalemia.[15] Canine ECG abnormalities include depression of the ST segment and prolongation of the QT interval (Figure 55-1).[16] Increased P wave amplitude, prolongation of the PR interval, and widening of the QRS complex may also occur. In addition, hypokalemia predisposes to digitalis-induced cardiac arrhythmias and causes the myocardium to become refractory to the effects of class I antiarrhythmic agents (lidocaine, quinidine, and procainamide).

55.3.3 Treatment of Hypokalemia

The main treatment objectives include replacing the potassium deficits and correcting the primary underlying disease process. Potassium gluconate powder is a convenient form of dietary supplementation for dogs and cats that is given orally in food twice daily at a recommended dosage of ¼ teaspoonful (2 mEq) per 4.5 kg body weight. The maintenance dosage should be titrated to effect. Its use is limited to animals that can be fed by mouth or by gastroenteral routes.

55.3.3.1

Box 55-1 Causes of Hypokalemia[3-8]

55.3.3.1.1

Disorders of Internal Balance (Redistribution)

Metabolic alkalosis

Insulin administration

Increased levels of catecholamines

β-Adrenergic agonist therapy or intoxication

Refeeding syndrome

55.3.3.1.2

Disorders of External Balance (Depletion)

Renal potassium wasting

Prolonged inadequate intake

Diuretic drugs

Osmotic or postobstructive diuresis

Chronic liver disease

Inadequate parenteral fluid supplementation

Aldosterone-secreting tumor

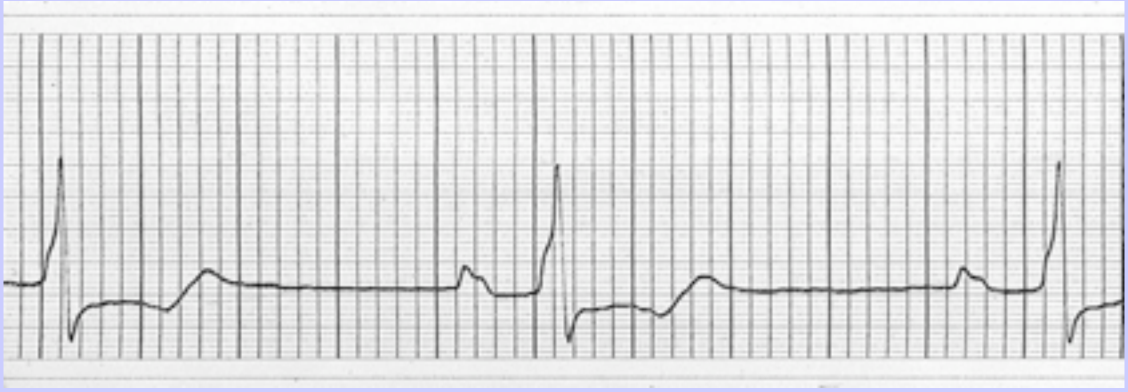
Prolonged vomiting associated with pyloric outflow obstruction

Diabetic ketoacidosis

Renal tubular acidosis

Severe diarrhea

Figure 55-1 Lead II electrocardiogram taken from a dog with a serum potassium measuring 2.1 mEq/L. Note the increased P wave amplitude, the depressed ST segment, and the depressed T waves.



Treatment of moderate (2.5 to 3 mEq/L) to severe (<2.5 mEq/L) hypokalemia in the anorectic or vomiting patient requires parenteral administration of potassium chloride solution (or potassium phosphate in hypophosphatemic patients; Table 55-1). The rate of potassium infusion should seldom exceed 0.5 mEq/kg/hr for mild to moderate hypokalemia.[17] In profoundly hypokalemic patients with normal or increased urine output (serum potassium <2 mEq/L), the rate can be increased cautiously to 1 to 1.5 mEq/kg/hr along with close ECG monitoring.[17] Conditions that may predispose an animal to adverse effects of a potassium infusion include oliguria and anuria, hypoaldosteronism (Addison's disease), and coadministration of potassium-sparing drugs. In a patient with metabolic acidosis, potassium chloride can be added to the buffer-containing intravenous fluids, whereas potassium chloride is added preferentially to normal saline solution for the patient with metabolic alkalosis.

It is important to remember that these values are only ranges that must be adjusted to each patient's pathophysiologic needs. This is exemplified by the severely oliguric or anuric animal requiring minimal 230 maintenance amounts of parenteral potassium chloride, in contrast with the polyuric ketoacidotic diabetic patient 231 receiving regular crystalline insulin, that will require much higher amounts. Animals with distributive shock should be resuscitated with an isotonic crystalloid solution before adding potassium chloride to the crystalloid fluid infusion. In the severely hypokalemic patient (serum potassium <2 mEq), it is prudent to begin potassium treatment during the rehydration period, either as a separate infusion or at a lower fluid rate in order to stay within acceptable guidelines for potassium infusion (0.5 to 1.5 mEq/kg/hr). Administration of sodium bicarbonate or insulin to hypokalemic diabetic patients should be postponed for the first 4 to 8 hours to correct the serum potassium level to greater than 3.5 mEq/L. Failure to do so can lead to marked hypokalemia.

Table 55-1 Guidelines for Routine Intravenous Supplementation of Potassium in Dogs and Cats

Serum Potassium Concentration (mEq/L)	mEq KCl to Add to 250 ml Fluid*	mEq KCl to Add to 1 L Fluid	Maximal Fluid Infusion Rate† (ml/kg/hr)
<2	20	80	6
2.1 to 2.5	15	60	8
2.6 to 3	10	40	12
3.1 to 3.5	7	28	18
3.6 to 5	5	20	25

From Greene RW, and Scott RC: Lower urinary tract disease. In Ettinger SJ, editor: *Textbook of veterinary internal medicine,* Philadelphia, 1975, Saunders.

* It is essential to shut off the flow valve to the patient and that the fluid container contents are thoroughly mixed during and after adding potassium to the parenteral fluids.

† So as not to exceed 0.5 mEq/kg/hr.

55.3.4 Anticipated Complications

Hyperkalemia can occur from excessive potassium supplementation. This is covered in the next section. Hypokalemic neuromuscular dysfunction is worsened and refractoriness to therapy may be evident when hypomagnesemia and hypocalcemia coexist. It is important to correct all serum electrolyte deficiencies to attain normal neuromuscular function (see Chapters 57 and 58, Magnesium Disorders and Phosphate Disorders, respectively).

55.4 HYPERKALEMIA

55.4.1 Definition and Causes

Hyperkalemia occurs when the serum potassium concentration exceeds 5.5 mEq/L and is considered life threatening at serum concentrations greater than 7.5 mEq/L. Hyperkalemia can result from four basic disturbances: increased intake or administration, translocation from the intracellular to the extracellular fluid space, decreased renal excretion, and an artifactual or pseudohyperkalemia (Box 55-2).

Excessive potassium supplementation (potassium chloride or potassium phosphate) in intravenous fluids or overly rapid rates of administration can lead to hyperkalemia. To avoid cardiotoxicity, under most circumstances the intravenous rate should not exceed 0.5 mEq/kg/hr. Hyperkalemia can also occur from the administration of packed red blood cells that are past the expiration date or angiotensin-converting enzymes, potassium-sparing diuretics, or nonselective β-blocking drugs combined with potassium supplementation.

An increased movement of potassium out of cells can lead to hyperkalemia, as seen with a mineral acidosis (uremic, respiratory, or induced by ammonium chloride, hydrogen chloride, or calcium chloride infusions) causing potassium to move out of the intracellular space in exchange for hydrogen ions. This extracellular translocation of potassium can also occur with snakebites, heat stroke, crushing injuries, or tumor lysis syndrome associated with chemotherapy and radiation in dogs with lymphosarcoma.[19,20] Hyperkalemia has also been reported in cats treated with thrombolytic agents for aortic thromboembolism as a result of reperfusion of the affected limb(s).[21]

Although osmotic diuresis decreases the total body potassium concentration in diabetic ketoacidosis, hyperkalemia may occur as a result of decreased cellular uptake of potassium secondary to insulin deficiency, extracellular translocation of potassium with water due to serum hyperosmolality (“solute drag”), increased protein catabolism, prerenal azotemia, and any coexisting renal impairment. Insulin therapy normalizes the serum potassium concentration by correcting the insulin deficiency and hyperosmolality while decreasing the need for protein catabolism.

Decreased urinary excretion secondary to renal or postrenal disease is the most common cause of hyperkalemia in small animal patients. In animals with complete urinary obstruction or uroabdomen, an ECG should be evaluated for evidence of hyperkalemia while the serum potassium concentration is determined. Intravenous, potassium-free fluids such as 0.9% saline should be administered, as indicated, and further steps to reduce serum potassium or reduce the cardiotoxic effects of hyperkalemia should be taken if cardiac arrhythmias are present (see Treatment of Hyperkalemia section).

Oliguria and anuria are most commonly associated with acute tubular damage, however oliguria can also occur with end-stage chronic renal failure. The distal tubule is dependent on both adequate glomerular filtration rate and urine flow to excrete potassium effectively. The severe reduction in both of these determinants with acute renal failure significantly impairs the ability of the distal tubule to excrete sufficient potassium. Attempts to restore a normal effective circulating volume are essential to improving urine output and urinary potassium excretion. If no urine is produced after fluid therapy, additional measures should be taken (e.g., furosemide or mannitol), in attempts to convert the oliguric or anuric patient to a nonoliguric state (see Chapters 135 and 180, Acute Renal Failure and Diuretics, respectively).

Patients with classic, severe hypoadrenocorticism typically have hyperkalemia and hyponatremia and a sodium-to-potassium ratio less than 27:1. An adrenocorticotropic hormone stimulation test is essential to differentiate this disease from acute renal failure, because these patients might also be azotemic. Natriuresis in the absence of 231
aldosterone leads to a reduced effective circulating volume, which further impairs distal tubule potassium 232
excretion. This volume depletion also leads to reduced renal perfusion, prerenal azotemia, and further potassium retention. Initial therapy should include restoration of the effective circulating volume with potassium-free or potassium-deficient fluids (see Chapter 76, Hypoadrenocorticism).

55.4.1.1 Box 55-2 Causes of Hyperkalemia

55.4.1.1.1 Increased Intake or Supplementation

Intravenous potassium-containing fluids

Expired RBC transfusion

Translocation from ICF to ECF

Mineral acidosis (NH_4Cl, HCl)

Diabetes mellitus with ketoacidosis or hyperosmolality

Acute tumor lysis syndrome

Extremity reperfusion following therapy for thromboembolism

55.4.1.1.2 Decreased Urinary Excretion

Anuric or oliguric renal failure

Urethral obstruction

Ruptured urinary bladder

Hypoadrenocorticism

Gastrointestinal disease (trichuriasis, salmonellosis, perforated duodenum)

Chylothorax with mechanical drainage

Drugs (ACE inhibitors, potassium-sparing diuretics, nonspecific β-blockers)

Pseudohyperkalemia

Thrombocytosis or leukocytosis

Akita dog and other dogs of Japanese origin

ACE, Angiotensin-converting enzyme; *ECF,* extracellular fluid; *HCl,* hydrogen chloride; *ICF,* intracellular fluid; *NH_4Cl,* ammonium chloride; *RBC,* red blood cell.

Gastrointestinal disease, especially that associated with trichuriasis, salmonellosis, or duodenal perforation, can be associated with hyperkalemia and a reduced sodium-to-potassium ratio (<27:1).[22,23] Chronic chylothorax managed by intermittent or continual drainage can result in hyperkalemia and hyponatremia.[24] In addition, these abnormalities were reported in a dog with a lung lobe torsion, another with a neoplastic pleural effusion, and three at-term pregnant Greyhounds.[25-27] Although the mechanism of hyperkalemia in such patients is unclear, a reduction in effective circulating volume and subsequent reduced distal renal tubular flow could lead to deficient urinary potassium excretion.

55.4.2 Consequences

Muscle weakness can occur when serum potassium concentrations exceed 7.5 mEq/L. Hyperkalemia may cause bradycardia or atrial standstill due to prolonged depolarization and repolarization of the myocardial conduction system. ECG findings do not correlate precisely with serum potassium concentrations; however, generalizations can be made as to the progression of waveform and conduction changes (Table 55-2).[18]

55.4.3 Pseudohyperkalemia

Potassium can be released from increased numbers of circulating blood cells, especially platelets and white blood cells, causing an artifactual increase in potassium termed *pseudohyperkalemia*. This is seen primarily in animals with severe thrombocytosis or leukocytosis. Pseudohyperkalemia can also be seen in Akita dogs (or other dogs of Japanese origin) secondary to in vitro hemolysis, because their erythrocytes have a functional sodium-potassium adenosine triphosphatase and, as such, have high intracellular potassium concentrations. This potassium is released and causes an artifactual hyperkalemia if hemolysis occurs in the serum blood tube. Confirmation of pseudohyperkalemia can be made by determining the plasma potassium concentration (blood collected in a heparinized tube) as this should not be affected by changes in platelet or white blood cell numbers.

55.4.4 Treatment of Hyperkalemia

An ECG should be performed in any patient with suspected or confirmed hyperkalemia. In asymptomatic animals with normal urine output, serum potassium concentrations between 5.5 and 6.5 mEq/L rarely warrant immediate therapy; however, the cause of the hyperkalemia should be investigated. In all hyperkalemic patients, exogenous potassium administration should be discontinued. Intravenous potassium-free or potassium-deficient isotonic crystalloids can be administered to promote diuresis, and this alone may be sufficient to correct mild hyperkalemia (≤6 mEq/L). Loop (furosemide 1 to 4 mg/kg) or thiazide (chlorothiazide 10 to 40 mg/kg, hydrochlorothiazide 2 to 4 mg/kg) diuretics can increase urinary potassium excretion; however, their use must follow rehydration. Drugs that promote hyperkalemia, such as angiotensin-converting enzyme inhibitors, β-adrenergic antagonists, and potassium-sparing diuretics, should be discontinued. Immediate therapy is directed toward reducing and antagonizing serum potassium in patients with severe ECG changes or when the serum potassium concentration exceeds 8 mEq/L. Ten percent calcium gluconate or calcium chloride can be administered to antagonize the cardiotoxic effects of hyperkalemia, but this has no effect on serum potassium concentrations. β-Adrenergic agonists, sodium bicarbonate, and dextrose with or without insulin can be administered to reduce serum potassium concentrations as described in Table 55-3. Peritoneal dialysis and hemodialysis will effectively treat hyperkalemia that is not responsive to the above-mentioned interventions.

Table 55-2 Electrocardiographic Changes With Hyperkalemia[18]

Serum Potassium Concentration	Electrocardiographic Change
>5.5 mEq/L	Peaked, narrow T wave
>6.5 mEq/L	Prolonged QRS complex and PR interval
	Depressed R wave amplitude
	Depressed ST segment
>7 mEq/L	Depressed P wave amplitude
>8.5 mEq/L	Atrial standstill
	Sinoventricular rhythm
>10 mEq/L	Biphasic QRS complex
	Ventricular flutter
	Ventricular fibrillation
	Ventricular asystole

Table 55-3 Treatment of Life-Threatening Hyperkalemia

Drug	Dosage	Mechanism of Action	Onset of Action
10% Calcium gluconate	0.5 to 1.5 ml/kg IV slowly over 5 to 10 minutes with ECG monitoring	Allows for decreased cardiacmuscle membrane potential but will not lower serum potassium	3 to 5 minutes
Sodium bicarbonate	1 to 2 mEq/kg IV slowly over 15 minutes	Causes metabolic alkalosis allowing for potassium to move intracellularly	15 minutes
25% Dextrose	0.7 to 1 g/kg IV over 3 to 5 minutes	Allows for translocation of potassium into the intracellular space	<1 hour
25% Dextrose with insulin	Regular insulin at *0.5 U/kg IV with IV dextrose at 2 g/U of insulin administered	As above	30 minutes
Terbutaline	0.01 mg/kg IV slowly	Stimulates Na^+/K^+-ATPase to cause translocation into the cell	20 to 40 minutes

ECG, Electrocardiographic; *IV*, intravenous; *Na^+/K^+-ATPase*, sodium-potassium adenosine triphosphatase.

* With hypoadrenocorticism the insulin dosage should be reduced to 0.25 U/kg IV because of the patient's predisposition to hypoglycemia.

55.5 SUGGESTED FURTHER READING*

SP DiBartola, HA de Morais: Disorders of potassium: hypokalemia and hyperkalemia. In SP DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders in small animal practice*. 2006, Philadelphia, Saunders, *A section of an excellent textbook providing extensive information on potassium disturbances including a good review of pathophysiology, causes of both hypokalemia and hyperkalemia, and management of such disorders*.

SK Theisen, SP DiBartola, J Radin, et al.: Muscle potassium content and potassium gluconate supplementation in normokalemic cats with naturally occurring chronic renal failure. *J Vet Intern Med*. **11**, 1997, 212, *Comparison of the long-term effects of oral potassium supplementation on muscle potassium content in normal cats and those with chronic renal failure*.

* See the CD-ROM for a complete list of references

56 Chapter 56 Calcium Disorders

Todd Green, DVM

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56.1 KEY POINTS

- Severe hypercalcemia or hypocalcemia can be lethal in dogs and cats, especially if extremes of serum calcium concentration develop rapidly.
- Disorders of hypocalcemia are encountered more commonly than are disorders of hypercalcemia.
- Hypocalcemia based on total serum calcium is often mild and less frequently requires calcium-specific management than does hypercalcemia.
- Toxicity of hypercalcemia is greatly magnified if the serum phosphorus concentration is also increased.
- No calcium-specific management is indicated when the total serum calcium is increased but the ionized calcium level is normal.
- No calcium-specific management is indicated when the total serum calcium is decreased, but the ionized calcium level is normal.
- Hypercalcemic crisis is most likely to be encountered when there is toxicity from excess vitamin D metabolites circulating in the body.
- Acute management of moderate to severe ionized hypercalcemia involves intravenous saline, furosemide, calcitonin, and glucocorticoids.
- Severe hypercalcemia may benefit from intermittent intravenous doses of bisphosphonates to decrease osteoclast function. Pamidronate is the first-choice bisphosphonate in veterinary medicine, but zoledronate is more potent and is achieving greater popularity among oncologists.
- In many instances, management of severe and symptomatic hypocalcemia involves the administration of immediate intravenous boluses of calcium salts followed by a continuous rate infusion to maintain normal serum ionized calcium levels.
- Ionized hypocalcemia occurs more frequently than predicted when only the total serum calcium is measured, especially in the critical care setting.

56.2 CALCIUM HOMEOSTASIS

Calcium is an important electrolyte that is crucial for numerous intracellular functions, extracellular functions, and skeletal bone support. Calcium is necessary for muscle contraction; ionized calcium mediates acetylcholine release during neuromuscular transmission. Calcium also stabilizes nerve cell membranes by decreasing membrane permeability to sodium. Because of the complexity of its functions, normal homeostatic control mechanisms attempt to keep serum calcium within a narrow range. When these homeostatic mechanisms are disrupted or overwhelmed, conditions of hypocalcemia and hypercalcemia can occur. Three primary forms of calcium exist in serum and plasma: ionized (free), protein bound, and complexed (calcium bound to phosphate, bicarbonate, lactate, citrate, oxalate).[1] The ionized form of calcium is the biologically active form in the body and is considered the most important indicator of functional calcium levels.

Calcium regulation is a complex process involving primarily parathyroid hormone (PTH), vitamin D metabolites, and calcitonin. These calcium regulatory hormones exert most of their effects on the intestine, kidney, and bone. PTH is synthesized and secreted by the chief cells of the parathyroid gland in response to hypocalcemia or low calcitriol levels (also known as $1,25(OH)_2D_3$, the principal active vitamin D metabolite). PTH is synthesized and secreted constantly at low rates to maintain serum ionized calcium levels within a narrow range in healthy animals. PTH secretion normally is inhibited by increased serum ionized calcium levels, as well as by increased concentration of circulating calcitriol. The principal action of PTH is to increase blood calcium levels through increased tubular reabsorption of calcium, increased osteoclastic bone resorption, and increased production of $1,25(OH)_2D_3$.

Vitamin D and its metabolites also play a central role in calcium homeostasis. Dogs and cats, unlike humans, photosynthesize vitamin D inefficiently in their skin and therefore depend on vitamin D in their diet.[2] After ingestion and uptake, vitamin D is first hydroxylated in the liver to $25(OH)D_3$ (calcidiol), and then it is further hydroxylated to calcitriol by the proximal tubular cells of the kidney. This final hydroxylation by the 1α-hydroxylase enzyme system to form active calcitriol is under tight regulation, and is influenced primarily by serum PTH, calcitriol, phosphorus, and calcium concentrations. Decreased levels of phosphorus, calcitriol, and calcium promote calcitriol synthesis, and increased levels of these substances all cause a decrease in calcitriol synthesis.

In terms of calcium homeostasis, calcitriol primarily acts on the intestine, bone, kidney, and parathyroid gland. In the intestine, calcitriol enhances the absorption of calcium and phosphate at the level of the enterocyte. In the bone, calcitriol promotes bone formation and mineralization by regulation of proteins produced by osteoblasts. In addition, calcitriol is also necessary for normal bone resorption because of its effect on osteoclast differentiation. In the kidney, calcitriol acts to inhibit the 1α-hydroxylase enzyme system, as well as to promote calcium and phosphorus reabsorption from the glomerular filtrate. In the parathyroid gland, calcitriol acts to inhibit the synthesis of PTH.

Although minor when compared with the effects of PTH and the vitamin D metabolites, calcitonin also plays a role in calcium homeostasis. It is produced in the thyroid gland in response to increased concentration of calcium following a calcium-rich meal and also during hypercalcemia. Calcitonin acts on the bone to inhibit osteoclastic bone resorption activity.

56.3 CALCIUM MEASUREMENT

56.3.1 Sample Handling Techniques

When sampling patients for calcium measurements, the patient should fast before collection if possible. Both serum and heparinized plasma samples can be used. When plasma samples are used, certain anticoagulants such as oxalate, citrate, and ethylenediaminetetraacetic acid should not be used, because they can dramatically lower calcium levels when measured in the laboratory. When measuring ionized calcium, serum is preferred over whole or heparinized blood. In addition, anaerobic samples are preferred for ionized calcium measurement, because pH can alter the concentration. In aerobic conditions, carbon dioxide can be lost, thus raising the pH in the sample. An alkalotic pH may increase the binding of calcium to protein and therefore artificially decrease the amount of ionized calcium in the sample. Aerobic samples can be used with reasonable diagnostic accuracy for ionized calcium measurement when sent to a referral laboratory, but species-specific correction formulas are needed that correct the sample pH to 7.40. Hand-held point-of-care analyzers consistently report ionized calcium values that are less than those from bench machines; this error increases with the magnitude of the calcium being measured.[3]

56.3.2 Ionized Versus Total Calcium

The calcium status of most animals usually is obtained first via measurement of total calcium. However, this parameter frequently does not reflect the ionized calcium concentration of the diseased patient,[4] especially in critically ill animals. Therefore, for accurate assessment of patient calcium status, measurement of ionized calcium is recommended. So-called correction formulas that are used to predict ionized calcium status from total serum calcium are quite inaccurate.[4]

56.4 HYPERCALCEMIA

Hypercalcemia can be caused by numerous disease processes (Box 56-1) and may exert toxic systemic effects in multiple organs when ionized hypercalcemia is present.

56.4.1 Clinical Signs and Diagnosis

Clinical signs associated with hypercalcemia loosely parallel the severity of calcium elevation. Common signs include polyuria and polydipsia (dogs, not cats), anorexia, constipation, lethargy, and weakness. Severely affected animals may display ataxia, obtundation, listlessness, muscle twitching, seizures, or coma. Bradycardia may be detected on physical examination, and electrocardiographic (ECG) monitoring may reveal a prolonged PR interval, widened QRS complex, shortened QT interval, shortened or absent ST segment, and a widened T wave. Bradyarrhythmias may progress to complete heart block, asystole, and cardiac arrest in severely affected animals. Other abnormalities may also be secondary to the underlying disease process causing the hypercalcemia.

Usually hypercalcemia is documented initially during measurement of serum total calcium as part of the animal's diagnostic workup for the clinical signs. Normal calcium values for dogs and cats can have a wide range and can differ from laboratory to laboratory, so reference values should be used from the laboratory to which the sample was submitted. In general, normal total calcium values are approximately 10 mg/dl for dogs and 9 mg/dl for cats. These values are for mature animals, because growing animals (dogs especially) can have higher total calcium values, likely secondary to normal bone growth. Once a diagnosis of hypercalcemia is suspected based on the total calcium value (>12 mg/dl in the dog and <11 mg/dl in the cat), an ionized calcium measurement should be performed to confirm the diagnosis.

A diagnosis of hypercalcemia is confirmed with an ionized calcium measurement greater than 6 mg/dl or 1.5 mmol/L in the dog or greater than 5.7 mg/dl or 1.4 mmol/L in the cat. The increase in ionized calcium typically parallels the increase in total serum calcium except in animals with renal failure, in which the increase in total calcium is caused by calcium binding with citrate, phosphate, or bicarbonate.

Once the hypercalcemia is confirmed, a thorough physical examination should be repeated. The clinician should palpate the anal sacs (dogs) and peripheral lymph nodes for any enlargement, perform a fundic examination, and do a thorough evaluation for any masses that may have been missed on initial examination (e.g., mammary tumors). Further diagnostic maneuvers should be tailored to the individual patient based on clinical signs, physical examination findings, initial laboratory testing, and suspected etiology, but may include a complete blood cell count, chemistry panel, urinalysis, imaging (thoracic radiographs, abdominal radiographs, abdominal ultrasonography, parathyroid ultrasonography), fine-needle aspiration with cytologic evaluation of any masses found, PTH measurement, PTH-related protein measurement, calcidiol measurement, calcitriol measurement, bone biopsy, and bone marrow aspiration.

56.4.1.1 Box 56-1 Differential Diagnoses for Hypercalcemia

56.4.1.1.1 Nonpathologic

Postprandial

Juvenile, growing animal

Laboratory error

Lipemia

56.4.1.1.2 Transient or Inconsequential

Hemoconcentration

Hyperproteinemia

Hypoadrenocorticism

56.4.1.1.3 Pathologic or Persistent/Consequential

56.4.1.1.3.1 Parathyroid Dependent

Primary hyperparathyroidism

- Adenoma
- Adenocarcinoma
- Hyperplasia
- Overdose recombinant PTH

56.4.1.1.3.2

Parathyroid Independent

Malignancy

Humoral hypercalcemia of malignancy

- Lymphosarcoma
- Anal sac apocrine gland adenocarcinoma
- Carcinoma (thyroid, prostate, mammary, etc.)
- Thymoma

Hematologic malignancies (bone marrow osteolysis, local osteolytic disease)

- Lymphosarcoma
- Multiple myeloma
- Leukemia
- Myeloproliferative disorders

Bone neoplasia (primary or metastatic)

Idiopathic hypercalcemia (cats)

Chronic renal failure

Calcinosis cutis—during recovery, especially after DMSO

Hypervitaminosis D

- Iatrogenic
- Plants (calcitriol glycosides)
- Rodenticide (cholecalciferol)
- Antipsoriasis creams (calcipotriene or calcipotriol)

Granulomatous disease (calcitriol synthesis)

  - Fungal
  - Injection site reaction

Acute renal failure

Skeletal lesions

  - Osteomyelitis
  - Hypertrophic osteodystrophy
  - Disuse osteoporosis
  - Bone infarction

Excessive oral calcium

  - Calcium-containing intestinal phosphate binders
  - Calcium supplementation (calcium carbonate)

Hypervitaminosis A

Raisin/grape toxicity

Modified from DiBartola SP: *Fluid, electrolyte, and acid-base disorders in small animal practice,* ed 3, St Louis, 2006, Saunders.*DMSO*, Dimethyl sulfoxide.

56.4.2 Differential Diagnoses

A list of differential diagnoses for hypercalcemia is presented in Box 56-1, with neoplasia-associated hypercalcemia being the most common cause in dogs. In cats, neoplasia is thought to be the third most common cause of hypercalcemia behind idiopathic hypercalcemia and renal failure. Serum phosphorus levels tend to be normal or low in animals with primary hyperparathyroidism or malignancies with an elevated PTH-related protein. A thorough discussion of the pathophysiology of hypercalcemia in various disease processes is beyond the scope of this chapter; however, a thorough understanding of these principles is important because they serve as a guide for diagnosis and treatment.[1]

56.4.3 Treatment of Hypercalcemia

The consequences of hypercalcemia can be severe and can affect multiple body systems including the central nervous system (CNS), gastrointestinal tract, heart, and kidneys. Therefore a timely diagnosis and rapid intervention are vital. However, there is no absolute calcium value that should serve as a guide for initiating aggressive treatment. Rather, intervention should be guided by multiple factors, including the magnitude of hypercalcemia, rate of development, stable or progressive disease, clinical signs associated with hypercalcemia, organ dysfunction (renal, cardiac, CNS), clinical condition of the patient, and the suspected etiology of the hypercalcemia (Figure 56-1). In addition, evaluation of phosphorus concentrations may help in guiding therapy, because a calcium-phosphorus product of greater than 60 represents increased risk for soft tissue mineralization.

Definitive treatment for hypercalcemia is removing the underlying cause. However, in many cases the cause is not readily apparent, and sometimes palliative therapy must be instituted before treating the primary disease (Table 56-1).

Acute therapy often involves the use of one or more of the following: intravenous fluids, diuretics (furosemide), glucocorticoids, and calcitonin (Figure 56-2). The fluid of choice for hypercalcemia therapy is 0.9% sodium chloride, because the additional sodium ions present competition for calcium and result in reduced renal tubular calcium reabsorption. In addition, 0.9% sodium chloride is calcium free, thus not adding to the calcium load on the body. Intravenous fluid therapy should be used to correct dehydration over 4 to 6 hours and then given at rates of at least 1.5 to 2 times maintenance (see Chapter 64, Daily Intravenous Fluid Therapy). Potassium supplementation often is needed with this fluid protocol (potassium 5 to 40 mEq/L) depending on serum potassium concentrations (see Chapter 55, Potassium Disorders). Judicious fluid therapy should be used in patients with cardiac disease or hypertension, because volume overload and pulmonary congestion may easily occur. Furosemide enhances urinary calcium loss but should not be used in volume-depleted animals. Suggested dosages of furosemide are 1 to 2 mg/kg IV, SC, PO q12h. A constant rate infusion (CRI) of 0.2 to 1 mg/kg/hr may occasionally be needed for several hours during a hypercalcemic crisis. Meticulous attention to fluid therapy needs is essential when this method is used to avoid serious volume contraction. It may prove beneficial to place a urinary catheter in order to match the amount of fluid administered with the amount of urinary losses to ensure adequate volume replacement.

Figure 56-1 Definition of hypercalcemic crisis.

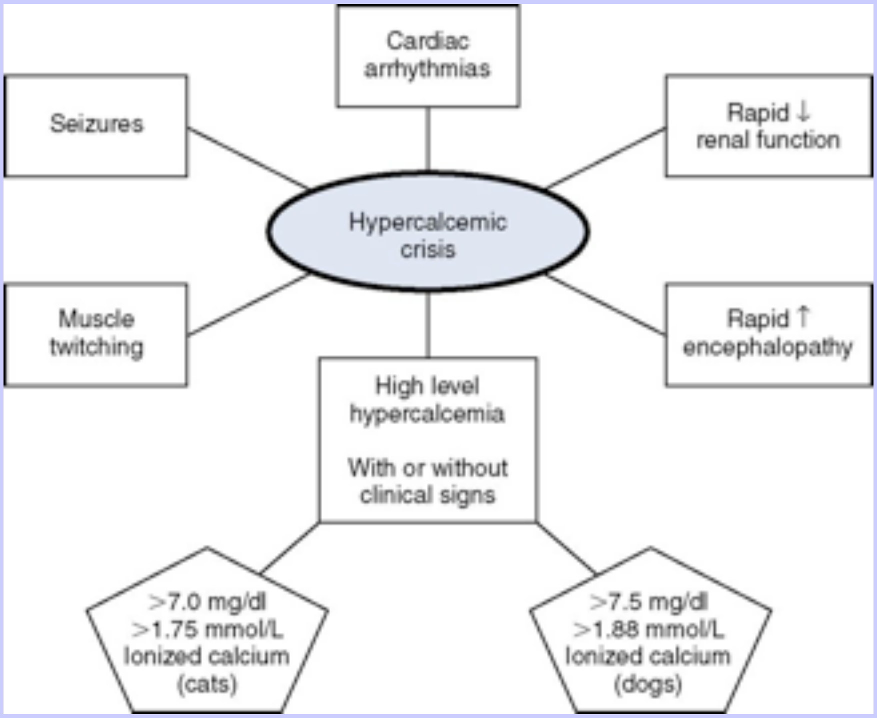


Table 56-1 Treatment of Hypercalcemia

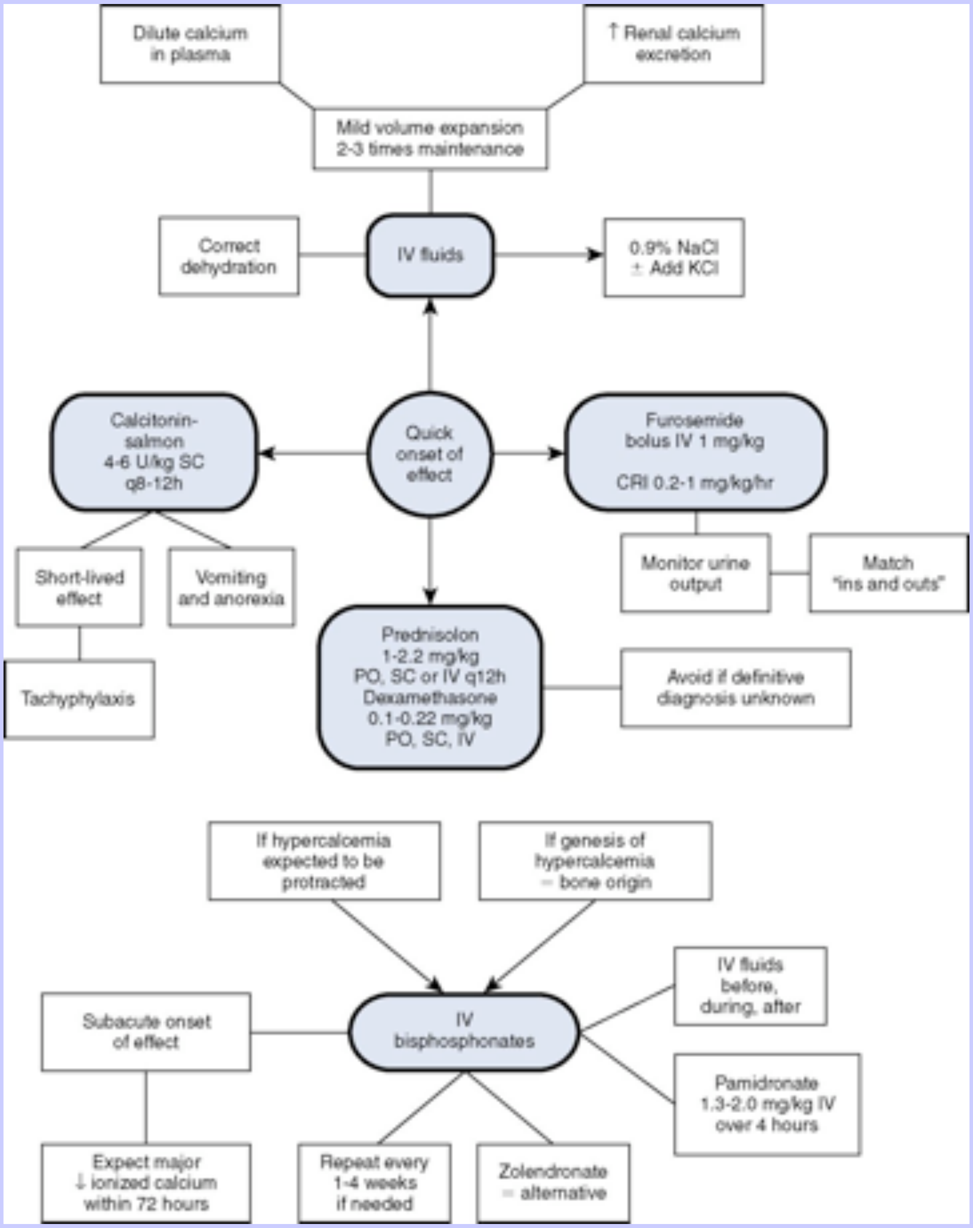
Treatment	Dosage	Indications	Comments
0.9% NaCl	90 to 120 ml/kg IV q24h	Moderate to severe hypercalcemia	Contraindicated in congestive heart failure and hypertension
Furosemide	1 to 2 mg/kg IV, SC, PO q12h CRI 0.2 to 1 mg/kg/hr	Moderate to severe hypercalcemia	Volume expansion necessary before administration Rapid onset
	CRI 0.2 to 1 mg/kg/hr		Rapid onset
Dexamethasone	0.1 to 0.22 mg/kg SC, IV q12h	Moderate to severe hypercalcemia	Use before identification of etiology may make definitive diagnosis difficult or impossible
Prednisone	1 to 2.2 mg/kg PO, SC, IV q12h	Moderate to severe hypercalcemia	Use prior to identification of etiology may make definitive diagnosis difficult or impossible
Calcitonin-salmon	4 to 6 IU/kg SC q8-12h	Hypervitaminosis D	Response may be short lived Vomiting may occur after multiple doses Rapid onset
Sodium bicarbonate	1 mEq/kg slow IV bolus (may give up to 4 mEq/kg total dosage)	Severe, life-threatening hypercalcemia	Requires close monitoring Rapid onset
Pamidronate	1.3 to 2.0 mg/kg in 150 ml 0.9% NaCl IV over 2 to 4 hr	Moderate to severe hypercalcemia	Expensive Delayed onset
Cinacalcet	No veterinary dosing published	Tertiary hyperparathyroidism Malignant primary hyperparathyroidism	May have future uses in veterinary medicine

Modified from DiBartola SP: *Fluid, electrolyte, and acid-base disorders in small animal practice*, ed 3, St Louis, 2006, Saunders.*CRI,* Constant rate infusion; *IV,* intravenous; *NaCl,* sodium chloride; *PO,* per os; *SC,* subcutaneous.

Glucocorticoids can cause a reduction in serum calcium concentration in many animals with hypercalcemia. Glucocorticoids lead to reduced bone resorption, decreased intestinal calcium absorption, and increased renal calcium excretion. The magnitude of decline with therapy depends on the cause of the hypercalcemia. Dexamethasone often is given at dosages of 0.1 to 0.22 mg/kg SC, IV q12h, or prednisone at dosages of 1 to 2.2 mg/kg PO, SC, IV q12h. However, in patients that have no definitive diagnosis for the hypercalcemia, calcitonin therapy should be considered instead of glucocorticoids, because the latter may interfere with obtaining an accurate cytologic or histopathologic diagnosis.

Calcitonin acts to decrease serum calcium concentrations by reducing the activity and formation of osteoclasts. Calcitonin-salmon can be used at a dosage of 4 to 6 IU/kg SC q8-12h. Vomiting may occur after several days of administration. Sodium bicarbonate can also be considered for crisis therapy because it decreases the ionized and total calcium; effects on the bound fractions of calcium have not been examined in this situation.[5] Sodium bicarbonate is given at a dosage of 1 mEq/kg IV as a slow bolus (up to 4 mEq/kg total dose) when patients are at risk for death (see Table 56-1). Acid-base status should be monitored closely to avoid inducing alkalemia or 236 other complications of bicarbonate therapy (i.e., paradoxical cerebral acidosis, hypernatremia). Peritoneal or 237 hemodialysis using calcium-free dialysate can be considered in cases refractory to traditional therapy. Fluid therapy should always be considered as the first treatment option, and other modalities added based on response to therapy and the status of the patient.

Figure 56-2 Treatment of critically ill patients with ionized hypercalcemia. *CRI,* Constant rate infusion; *IV,* intravenous; *PO,* per os; *SC,* subcutaneous.


Dilute calcium in plasma
↑ Renal calcium excretion
Mild volume expansion 2-3 times maintenance
Correct dehydration
IV fluids
0.9% NaCl ± Add KCl
Calcitonin-salmon 4-6 U/kg SC q8-12h
Quick onset of effect
Furosemide bolus IV 1 mg/kg
CRI 0.2-1 mg/kg/hr
Short-lived effect
Vomiting and anorexia
Monitor urine output
Match "ins and outs"
Tachyphylaxis
Prednisolon 1-2.2 mg/kg PO, SC or IV q12h Dexamethasone 0.1-0.22 mg/kg PO, SC, IV
Avoid if definitive diagnosis unknown
If hypercalcemia expected to be protracted
If genesis of hypercalcemia = bone origin
IV fluids before, during, after
Subacute onset of effect
IV bisphosphonates
Pamidronate 1.3-2.0 mg/kg IV over 4 hours
Expect major ↓ ionized calcium within 72 hours
Repeat every 1-4 weeks if needed
Zolendronate = alternative

Subacute or long-term treatment to decrease calcium levels may be needed in some cases rather than acute rescue therapy. Glucocorticoids and furosemide can be given for long-term therapy and are usually administered orally. In addition, subcutaneous fluids (0.9% sodium chloride) can be given at dosages of 75 to 100 ml/kg q24h as needed.

Bisphosphonates are a class of drugs that have been used in veterinary medicine for management of hypercalcemia.[4] These drugs decrease osteoclastic activity, thus decreasing bone resorption. Bisphosphonates often take 1 to 2 days to inhibit bone resorption, so they are not considered drugs of choice for acute or crisis therapy.[6] Pamidronate has been the most commonly used bisphosphonate in veterinary medicine for management of hypercalcemia; zoledronate is more potent than pamidronate and can be considered for use in selected patients. Pamidronate can be given intravenously at dosages of 1.3 to 2 mg/kg in 150 ml 0.9% saline as a 2-hour to 4-hour infusion.[7] This dose can be repeated in 1 week, if needed, but the salutary effect may last for 1 month in some instances. Oral alendronate at 1 to 3 mg/kg/week may be prescribed for the chronic treatment of idiopathic hypercalcemia in cats, but it is not as effective as intravenous bisphosphonate therapy in the acute setting. Oral bisphosphonates can cause esophageal irritation and have been reported to cause abdominal discomfort, nausea, and vomiting in humans.[8]

Calcimimetics belong to a new class of drugs that will likely have future use in veterinary medicine to treat some cases of hypercalcemia in which the underlying cause cannot be treated adequately by other means (tertiary hyperparathyroidism, primary hyperparathyroidism due to carcinoma). These drugs activate the calcium sensing receptor and thus decrease PTH secretion. Cinacalcet has been marketed for use in humans to treat renal secondary hyperparathyroidism and nonsurgical primary hyperparathyroidism.

56.5 HYPOCALCEMIA

Decreased total serum calcium is a relatively common electrolyte disturbance in critically ill dogs and cats. In one study the prevalence of ionized hypocalcemia in sick dogs was 31%.[4]

56.5.1 Clinical Signs and Diagnosis

A list of clinical signs that occur with hypocalcemia is presented in Box 56-2. Signs of hypocalcemia are often not seen until serum total calcium concentrations are less than 6.5 mg/dl (<4 mg/dl or <1 mmol/L ionized calcium), and many animals show few signs even with lower calcium levels. Most animals with rapid development of hypocalcemia show clinical signs. Severely affected animals may have decreased inotropy and chronotropy (bradycardia), and ECG abnormalities may include a prolonged QT interval (due to prolonged ST segment), deep, wide T waves, or atrioventricular block.

56.5.1.1 Box 56-2 Clinical Signs Associated With Hypocalcemia

56.5.1.1.1 Common

None

Muscle tremors or fasciculations

Facial rubbing

Muscle cramping

Stiff gait

Behavioral change

- Restlessness or excitation
- Aggression
- Hypersensitivity to stimuli
- Disorientation

56.5.1.1.2 Occasional

Seizures

Panting

Pyrexia

Lethargy

Anorexia

Prolapse of third eyelid (cats)

Posterior lenticular cataracts

Tachycardia or ECG alterations (i.e., prolonged QT interval)

56.5.1.1.3 Uncommon

Polyuria or polydipsia

Hypotension

Respiratory arrest or death

Modified from DiBartola SP: *Fluid, electrolyte, and acid-base disorders in small animal practice,* ed 3, St Louis, 2006, Saunders. *ECG,* Electrocardiographic.

Hypocalcemia usually is discovered fortuitously after routine measurement of serum total calcium concentration. Hypocalcemia is defined as a total calcium concentration less than 8 mg/dl in dogs, and less than 7 mg/dl in cats. When hypocalcemia is diagnosed via total calcium concentrations, it should always be confirmed with an ionized calcium measurement. Using ionized calcium concentrations, hypocalcemia is defined as less than 5 mg/dl (1.25 mmol/L) in dogs, and less than 4.5 mg/dl (1.1 mmol/L) in cats.

After a diagnosis of hypocalcemia is confirmed, other diagnostic strategies such as complete blood cell count, chemistry panel, urinalysis, PTH measurement, and vitamin D metabolite measurements should all be considered.

56.5.2 Differential Diagnoses

A list of differential diagnoses for hypocalcemia is presented in Box 56-3. The most common cause of a total serum hypocalcemia is hypoalbuminemia. However, the hypocalcemia is usually mild and usually no signs are seen that are attributable to the hypocalcemia with this condition. Correction formulas have been advocated in the past to correct calcium levels for a low albumin, but these formulas do not accurately predict ionized calcium concentrations and are therefore not recommended.[4]

56.5.2.1 Box 56-3 Differential Diagnoses for Hypocalcemia

- Hypoalbuminemia
- Chronic renal failure
- Eclampsia
- Acute renal failure
- Pancreatitis
- Soft tissue trauma or rhabdomyolysis
- Hypoparathryoidism
    - Primary hypoparathryoidism
        - Idiopathic
        - Iatrogenic (postoperative bilateral thryoidectomy)
    - After sudden reversal of chronic hypercalcemia
    - Secondary to magnesium depletion, retention

- Ethylene glycol
- Phosphate enema
- Bicarbonate administration
- Improper sample anticoagulant (EDTA)
- Infarction of parathyroid gland adenoma
- Rapid IV infusion of phosphates
- Acute calcium-free IV infusion
- Intestinal malabsorption, PLE, starvation
- Hypovitaminosis D
- Blood transfusion (citrated anticoagulant)
- Hypomagnesemia (PTH secretion and receptor effects)
- Nutritional secondary hyperparathyroidism
- Acute tumor lysis syndrome
- Chelating agents
    - CaEDTA, dimercaprol (British anti-Lewisite), D-penicillamine, and meso-2,3-dimercaptosuccinic acid (succimer, IV radiocontrast)
- Excessive bisphosphonate treatments

Modified from DiBartola SP: *Fluid, electrolyte, and acid-base disorders in small animal practice,* ed 3, St Louis, 2006, Saunders. *EDTA*, Ethylenediamine tetraacetic acid; *PLE*, protein-losing enteropathy; *PTH*, parathyroid hormone.

Renal failure appears to be the second most common cause of hypocalcemia in dogs. Primary hypoparathyroidism is the one condition that will require long-term calcium-specific treatment. If the serum phosphorus level is high, the most likely diagnoses to rule out include renal failure, pancreatitis with or without prerenal azotemia, excessive intake of phosphorus, and primary hypoparathyroidism.

56.5.3 Treatment

The consequences of untreated severe ionized hypocalcemia can be life threatening because of myocardial failure and respiratory arrest. The decision to treat hypocalcemia should be based on multiple factors, including severity of clinical signs, speed of development of hypocalcemia, and the etiology of the primary disease. Hypermagnesemia and hypomagnesemia can impair the secretion of PTH, and PTH actions on its receptor, so measurement of serum magnesium (preferably ionized magnesium) is important, especially in animals with refractory hypocalcemia.

Patients with decreased total calcium concentrations but normal ionized calcium concentrations require no treatment. If a decreased ionized calcium concentration is found, the clinician must decide if therapy is warranted. If the patient is stable, no clinical signs referable to hypocalcemia are documented, and the ionized calcium is not progressively decreasing, then it is reasonable to consider not treating these patients. Patients with a severe decrease in ionized calcium concentration warrant calcium-specific treatment regardless of clinical signs.[9,10] Therapy may also be initiated in an asymptomatic patient with moderate ionized hypocalcemia that is decreasing progressively to prevent the development of signs. Patients with clinical signs attributed to hypocalcemia clearly should receive calcium-specific rescue therapy.

Treatment of hypocalcemia can be divided into acute and subacute to long term. As with all cases of hypocalcemia, attempts should always be made to treat the primary disease causing the disorder. Most cases of hypocalcemia do not require long-term therapy, with hypoparathyroidism being the exception. Many cases will require acute treatment, especially those with tetany, seizures, or muscle fasciculations. Therapy typically involves the administration of calcium salts, as well as vitamin D metabolites.

For acute therapy, calcium should be administered intravenously to effect over a 10- to 20-minute period. Calcium gluconate and calcium chloride are both available for treatment, but calcium gluconate is preferred because it is not irritating if injected perivascularly (unlike calcium chloride). Calcium salts should never be given subcutaneously, because they can cause severe skin necrosis and abscess formation. Calcium gluconate (10% solution, calcium 9.3 mg/ml) can be given at dosages of 0.5 to 1.5 ml/kg IV to effect. Heart rate and ECG should be monitored closely during administration to look for bradycardia, a prolonged PR interval, widened QRS complex, shortened QT interval, elevated, shortened, or absent ST segment, and a widened T wave, all of which may indicate cardiac toxicity. It is important to note that it may take up to 30 to 60 minutes for all clinical signs to resolve after correction of hypocalcemia, and some behavioral changes and panting may persist during this time.

For subacute management, the initial bolus of calcium salts often needs to be followed with a CRI of calcium, especially if the hypocalcemia is expected to persist. A CRI of elemental calcium can be delivered at a rate of 1 to 3 mg/kg/hr IV based on the severity of hypocalcemia to maintain normal calcium levels until oral calcium administration and or vitamin D metabolites can be used to control serum calcium concentrations. Vitamin D metabolites should also be started early if the hypocalcemia is expected to persist, because it may take several days for intestinal calcium transport to be maximized. Calcitriol is the preferred active vitamin D metabolite because it has a quick onset of action, short plasma half-life, and relatively short biologic effect half-life (important if overshoot hypercalcemia occurs). Calcitriol is dosed at 20 to 30 ng/kg q24h for 3 to 4 days for induction, then 5 to 15 ng/kg q24h for maintenance therapy, titrated to the desired level of serum calcium concentration.

For long-term therapy (e.g., primary hypoparathyroidism), oral calcium usually is needed to control serum calcium levels. It should be noted, however, that the goal of therapy with hypoparathyroidism is not to return calcium levels completely to normal, because this can have deleterious effects (hypercalciuria despite normocalcemia in the absence of basal effects that PTH normally has on renal tubules). One should aim to control signs and correct calcium levels to just below normal. Many forms of oral calcium are available (calcium carbonate, calcium lactate, calcium chloride, calcium gluconate) and all are dosed at 25 to 50 mg/kg q24h. Calcium carbonate is the most common form of calcium used and is generally well tolerated. Calcitriol can also be used at the previously mentioned dosages.

56.6 SUGGESTED FURTHER READING[*]

KJ Drobatz, D Hughes: Concentration of ionized calcium in plasma from cats with urethral obstruction. *J Am Vet Med Assoc*. **211**, 1997, 1392, *An article emphasizing that ionized calcium can be disproportionately lower than thought when only total serum calcium concentrations are considered.*

RA Hostutler, DJ Chew, JQ Jaeger, et al.: Uses and effectiveness of pamidronate disodium for treatment of dogs and cats with hypercalcemia. *J Vet Intern Med*. **9**, 2005, 29, *An article providing some examples for the safety and effectiveness of treatment with IV pamidronate in mostly dogs with hypercalcemia.*

PA Schenck, DJ Chew, LA Nagode, TJ Rosol: Disorders of calcium. In SP DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 3, 2006, Saunders, St Louis, *An exhaustive review of calcium physiology and disorders of calcium metabolism that are associated with hypercalcemia and hypocalcemia.*

[*] See the CD-ROM for a complete list of references

57 Chapter 57 Magnesium Disorders

Linda G. Martin, DVM, MS, DACVECC

57.1 KEY POINTS

- Hypomagnesemia is a common electrolyte disorder in critically ill veterinary patients.
- Given that less than 1% of total body magnesium is located in the serum, serum magnesium concentrations do not always reflect total body magnesium stores. Consequently, a normal serum magnesium concentration can occur when there is a total body magnesium deficiency.
- Magnesium homeostasis is primarily a function of intestinal absorption and urinary excretion; therefore hypomagnesemia is almost always caused by disturbances in one or both of these organ systems.
- Most cases of hypermagnesemia involve a component of renal insufficiency.
- Severe hypomagnesemia and hypermagnesemia cause clinical signs associated with the cardiovascular and neuromuscular systems.

57.2 INTRODUCTION

For more than a decade, there has been a growing interest in the clinical effects and therapeutic role of magnesium in veterinary medicine. Magnesium disorders are common in both feline and canine critically ill patients. Increased morbidity, mortality, and prevalence of concurrent electrolyte disorders occur in critically ill animals with altered total serum magnesium concentrations when compared with normomagnesemic critically ill animals.[1-3]

Magnesium is the second most abundant intracellular cation, exceeded only by potassium. The vast majority of magnesium is found in bone and muscle. Sixty percent of the total body magnesium content is present in bone, incorporated into the crystal mineral lattice or in the surface-limited exchangeable pool. This pool consists of magnesium that is in equilibrium with the magnesium ions in the extracellular fluid and serves as a reservoir for maintenance of the extracellular magnesium concentration. Twenty percent is located in skeletal muscle and the remainder is located in other tissues, primarily the heart and liver. Less than 1% of total body magnesium is present in the serum.[4,5] In the serum, magnesium exists in three distinct forms: an ionized fraction, an anion-complexed fraction, and a protein-bound fraction. The ionized fraction is thought to be the physiologically active component and accounts for approximately 66% and 63% of the total serum magnesium concentration in cats and dogs, respectively. Approximately 4% and 6% are complexed to compounds such as phosphate, bicarbonate, sulfate, citrate, and lactate in cats and dogs, respectively. The remaining 30% and 31% of total serum magnesium are bound to protein (primarily albumin) in cats and dogs, respectively.[6,7]

Magnesium is required for many metabolic functions, most notably those involved in the production and use of adenosine triphosphate (ATP). This electrolyte is a coenzyme for the membrane-bound sodium-potassium ATPase pump and functions to maintain the sodium-potassium gradient across all membranes. Calcium ATPase and proton pumps also require magnesium. Magnesium is also essential for protein and nucleic acid synthesis, regulation of vascular smooth muscle tone, cellular second messenger systems, and signal transduction. In addition, data suggest that magnesium exerts an important influence on lymphocyte activation, cytokine production, and systemic inflammation.[8-10]

Magnesium homeostasis is achieved through intestinal absorption and renal excretion. Absorption occurs primarily in the small intestine (jejunum and ileum) with little or none occurring in the large intestine. The loop of Henle is the main site of magnesium absorption in the kidney. The kidney appears to be the main regulator of serum magnesium concentration and total body magnesium content.[8] This is achieved by both glomerular filtration and tubular reabsorption.[5] Renal magnesium excretion will increase in proportion to the load presented to the kidney; conversely, the kidney conserves magnesium in response to a deficiency.[8]

Lactation appears to play a role in gut and renal handling of magnesium. Increased levels of parathyroid hormone, in addition to calcium concentration, most likely participate in magnesium conservation during lactation to supply the mammary glands with a sufficient amount.[11] No primary regulatory hormone has been identified for magnesium homeostasis, although the parathyroid, thyroid, and adrenal glands are likely involved.[12]

57.3 HYPOMAGNESEMIA

Most magnesium-related disorders are caused by conditions that lead to the depletion of total body stores. Hypomagnesemia is a common electrolyte abnormality in both canine and feline intensive care unit patients.[1-3] However, this electrolyte disorder appears to be less common in the general canine hospital population.[13] Ionized hypomagnesemia has been documented in perioperative feline renal transplant recipients, as well as cats with diabetes mellitus and diabetic ketoacidosis.[14,15] Other evidence suggests that animals on peritoneal dialysis, dogs with congestive heart failure being treated with furosemide, dogs with protein-losing enteropathy, and lactating dogs are also at risk for hypomagnesemia.[16-19]

57.3.1 Causes

Causes of magnesium deficiency are both numerous and complex. Three general categories are involved: 240
decreased intake, increased losses, and alterations in distribution. Potential causes are listed in Box 57-1. 241
Decreased dietary intake, if sustained for several weeks, can lead to significant magnesium depletion. In addition, catabolic illness and prolonged intravenous fluid therapy or parenteral nutrition without sufficient magnesium supplementation can contribute to depletion.[4,8,16]

57.3.1.1 Box 57-1 Causes of Hypomagnesemia

I **Decreased Intake**
    A Inadequate nutritional intake
    B Prolonged intravenous fluid therapy or parenteral nutrition without magnesium replacement
II **Increased Losses**
    A Gastrointestinal
        1 Malabsorption syndromes

        2 Extensive small bowel resection
        3 Chronic diarrhea
        4 Inflammatory bowel disease
        5 Cholestatic liver disease
    B Renal
        1 Intrinsic tubular disorders
            a Glomerulonephritis
            b Acute tubular necrosis
            c Postobstructive diuresis
            d Drug-induced tubular injury
                (1) Aminoglycosides
                (2) Amphotericin B
                (3) Cisplatin
                (4) Cyclosporine
        2 Extrarenal factors influencing renal magnesium handling
            a Diuretic-induced states
                (1) Furosemide
                (2) Thiazides
                (3) Mannitol
            b Digitalis administration
            c Diabetic ketoacidosis
            d Hyperthyroidism
            e Primary hyperparathyroidism
    C Lactation

III **Alterations in Distribution**

    A Extracellular to intracellular shifts
        1 Glucose, insulin, or amino acid administration

- B Chelation
    - 1 Elevation in circulating catecholamines
        - a Sepsis or shock
        - b Trauma
        - c Hypothermia
    - 2 Massive blood transfusion
- C Sequestration
    - 1 Pancreatitis

Magnesium losses can occur through the gastrointestinal(GI) tract, kidneys, or both. Because magnesium balance is primarily a function of intestinal absorption and urinary excretion, depletion is almost always caused by disturbances in one or both organ systems. Increased GI losses can result from inflammatory bowel disease, malabsorptive syndromes, cholestatic liver disease, or other diseases that cause prolonged diarrhea. Fluid from the intestinal tract contains a high concentration of magnesium. For this reason, patients with protracted episodes of large-volume diarrhea are prone to significant magnesium depletion.[4,9]

Because the kidney is the primary pathway of magnesium excretion, it often serves as a focal point for the development of hypomagnesemia through urinary loss. Acute renal dysfunction as a consequence of glomerulonephritis or the nonoliguric phase of acute tubular necrosis is often associated with a rise in the fractional excretion of magnesium. A number of endocrinopathies are also associated with an increase in the fractional excretion of magnesium, including diabetic ketoacidosis and hyperthyroidism.[9,15]

Numerous drugs administered to emergency and critically ill patients can increase renal magnesium loss. Most of the commonly administered diuretic agents (furosemide, thiazides, mannitol) and cardiac glycosides induce hypomagnesemia by increasing urinary excretion. Other drugs such as aminoglycosides, amphotericin B, cisplatin, and cyclosporine predispose to renal tubular injury and excessive magnesium loss.[4,8]

Disease states or therapeutic modalities can cause the redistribution of circulating magnesium by producing extracellular to intracellular shifts, chelation, or sequestration. Administration of glucose, insulin, or amino acids cause magnesium to shift intracellularly. Also, catecholamine elevations in animals with sepsis, trauma, or hypothermia may cause ionized hypomagnesemia. It appears that β-adrenergic stimulation of lipolysis generates free fatty acids that chelate magnesium, thereby producing insoluble salts. In addition, citrated blood products can avidly chelate magnesium ions when administered in large quantities. In acute pancreatitis, magnesium can form insoluble soaps, and magnesium sequestration may occur in areas of fat necrosis surrounding the pancreas.[4,8]

57.3.2 Clinical Signs

Clinical signs of magnesium depletion are often related to its effects on the cell membrane that result in changes in resting membrane potential, signal transduction, and smooth muscle tone. The effects of magnesium on the myocardium are linked to its role as a regulator of other electrolytes, primarily calcium and potassium. For this reason, one of the most dramatic clinical signs associated with hypomagnesemia is cardiac arrhythmias, including atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, and ventricular fibrillation. Hypomagnesemia also predisposes patients to digoxin-induced arrhythmias. Magnesium depletion not only enhances digoxin uptake by the myocardium, but also inhibits the myocardial sodium-potassium ATPase pump, as does digoxin. Before overt arrhythmia development, subtle electrocardiographic (ECG) changes may be seen. These include prolongation of the PR interval, widening of the QRS complex, depression of the ST segment, and peaking of the T wave. In addition to these changes, hypomagnesemia can cause hypertension, coronary artery vasospasm, and platelet aggregation.[9,20]

Hypomagnesemia can cause various nonspecific neuromuscular signs. Concurrent hypocalcemia and hypokalemia may also contribute. Magnesium deficiency increases acetylcholine release from nerve terminals and enhances the excitability of nerve and muscle membranes. It also increases the intracellular calcium content in skeletal muscle. Clinical manifestations of magnesium deficiency can include generalized muscle weakness, muscle fasciculations, ataxia, and seizures. Esophageal or respiratory muscle weakness can be manifested as dysphagia or dyspnea, respectively.[4,9]

Because magnesium is necessary for the movement of sodium, potassium, and calcium into and out of cells, other manifestations of hypomagnesemia include metabolic abnormalities such as concurrent hypokalemia, hyponatremia, and hypocalcemia. Concurrent hypokalemia that is refractory to aggressive potassium supplementation may be due to magnesium deficiency causing excessive potassium losses through the kidneys. When hypokalemia is refractory to potassium supplementation, assessment of magnesium status and subsequent magnesium supplementation are recommended. Hypocalcemia is another manifestation of magnesium deficiency. Because hypomagnesemia impairs parathyroid hormone release and enhances calcium movement from extracellular fluid to bone, hypocalcemia frequently accompanies magnesium depletion. Therefore clinical signs of hypocalcemia are often observed in patients with magnesium deficiency.[4,9]

57.3.3 Diagnosis

Magnesium deficiency should be suspected in patients predisposed to its development (disease processes or therapeutic modalities that can lead to hypomagnesemia) and exhibiting clinical signs and laboratory features consistent with magnesium depletion. Determination of total serum magnesium concentration is usually the most readily available technique for estimation of magnesium status. However, the precise clinical diagnosis of hypomagnesemia can be difficult. Because more than 99% of total body magnesium is located in the intracellular compartment, total serum concentrations do not always reflect total body stores. Therefore a normal total serum magnesium concentration can occur in an animal with a total body magnesium deficiency.[4,5] However, a low total serum concentration in a patient at risk for deficiency is usually significant. The reported reference range for total serum magnesium is 1.89 to 2.51 mg/dl in dogs, and 1.75 to 2.99 mg/dl in cats.[3,15]

The ionized magnesium concentration is thought to provide a more accurate reflection of intracellular ionized magnesium status and represents the “active” component. Ionized magnesium appears to equilibrate rapidly across the cell membrane; thus extracellular ionized magnesium values may be more reflective of intracellular stores. The canine reference range for ionized magnesium is 0.43 to 0.6 mmol/L, and the feline reference range is 0.43 to 0.7 mmol/L.[7]

57.3.4 Therapy

The amount and route of magnesium replacement depends on both the degree of hypomagnesemia and on the patient's clinical condition. Mild hypomagnesemia may resolve with management of the underlying disorder and modification of intravenous fluid therapy. Animals receiving long-term diuretic and digoxin therapy may benefit from oral magnesium supplementation. Supplementation should be considered if total serum magnesium concentrations are lower than 1.5 mg/dl and at any level if clinical signs (cardiac arrhythmias, muscle tremors, refractory hypokalemia) are present. Renal function and cardiac conduction must be assessed before magnesium administration. Because magnesium is excreted primarily by the kidneys, the dosage should be reduced by 50% in azotemic patients and serum concentrations should be monitored frequently to prevent hypermagnesemia. Magnesium prolongs conduction through the AV node. Therefore any patient with cardiac conduction disturbances should have judicious supplementation and continuous ECG monitoring.

Both sulfate and chloride salts are available for parenteral supplementation. The intravenous route is preferred for rapid repletion of magnesium concentrations. (The intramuscular route is generally painful.) An initial dosage of 0.5 to 1 mEq/kg q24h can be administered by continuous rate infusion in 0.9% sodium chloride or 5% dextrose in water. A lower dosage of 0.3 to 0.5 mEq/kg q24h can be used for an additional 3 to 5 days. For management of life-threatening ventricular arrhythmias, a dose of 0.15 to 0.3 mEq/kg of magnesium diluted in normal saline or 5% dextrose in water can be administered slowly over 5 to 15 minutes.[21] Parenteral administration of magnesium sulfate may result in hypocalcemia due to chelation of calcium with sulfate. Therefore magnesium chloride should be given if hypocalcemia is also present. Other side effects of magnesium therapy include hypotension, atrioventricular block, and bundle branch blocks. Adverse effects usually are associated with intravenous boluses rather than continuous rate infusions.

Chloride, gluconate, oxide, and hydroxide salts are available for oral administration. The suggested dosage is 1 to 2 mEq/kg q24h. The main side effect of this route is diarrhea.[21]

57.4 HYPERMAGNESEMIA

Hypermagnesemia appears to be a less common and simpler clinical entity than hypomagnesemia. Because large quantities of magnesium can be eliminated easily by the kidneys, it is unusual to encounter hypermagnesemia in the absence of azotemia. Unlike magnesium depletion, normal serum concentrations cannot hide increased body stores.

57.4.1 Causes

Conditions in which hypermagnesemia has been noted include renal failure, endocrinopathies, and iatrogenic overdose, especially in patients with impaired renal function. It appears that absolute magnesium excretion falls as glomerular filtration rate declines, so it is not surprising that most patients with hypermagnesemia have some degree of renal insufficiency. In general, the degree of hypermagnesemia parallels the degree of renal failure. Acute renal failure is more likely to be associated with clinically significant hypermagnesemia than chronic renal failure, but it may occur in the latter.[5]

Several endocrinopathies may be associated with hypermagnesemia. These diseases include hypoadrenocorticism, hyperparathyroidism, and hypothyroidism. In comparison with renal failure, these diseases cause hypermagnesemia less frequently and to a milder degree. The mechanisms that lead to hypermagnesemia are not well understood in these endocrine disorders. The prerenal azotemic state present in most patients with hypoadrenocorticism may contribute to hypermagnesemia.[22]

Improper dosing of magnesium replacement therapy or lack of consideration of the underlying renal function generally plays a role in iatrogenic hypermagnesemia. Many cathartics, laxatives, and antacids contain magnesium, so care should be exercised if multiple doses are given to a patient with underlying renal disease. Sorbitol-containing cathartics are advised when patients require multiple doses to detoxify the GI tract or have renal disease.[5,20]

57.4.2 Clinical Signs

Nonspecific clinical signs of hypermagnesemia include lethargy, depression, and weakness. Other clinical signs reflect the electrolyte's action on the nervous and cardiovascular systems. Hypermagnesemia usually results in varying degrees of neuromuscular blockade. One of the earliest clinical signs of magnesium toxicity is hyporeflexia. Profound magnesium toxicity has been associated with respiratory depression secondary to respiratory muscle paralysis. Severe respiratory depression can result in hypoventilation and subsequent hypoxemia. An absent menace and palpebral reflex have been reported in one dog and one cat that developed acute hypermagnesemia secondary to iatrogenic overdose.[23] In addition to this, hypermagnesemia can lead to blockade of the autonomic nervous system and vascular collapse.[20,22]

Cardiovascular effects of hypermagnesemia result in ECG changes including prolongation of the PR interval and widening of the QRS complex. This is due to delayed atrioventricular and interventricular conduction. Bradycardia can occur in hypermagnesemic patients. At severely high serum magnesium concentrations, complete heart block and asystole can occur. Ectopy does not appear to be enhanced by elevated serum magnesium concentrations. Hypermagnesemia has also been reported to produce hypotension secondary to relaxation of vascular resistance vessels. Myocardial contractility is probably not affected by hypermagnesemia. Additionally, hypermagnesemia may impair platelet function and coagulation.[22]

57.4.3 Diagnosis

Unlike magnesium deficiency, normal serum concentrations cannot hide increased magnesium stores. Total serum magnesium concentrations greater than 2.99 mg/dl in cats and 2.51 mg/dl in dogs are considered indicative of hypermagnesemia.[3,15] Ionized magnesium concentrations above 0.7 mmol/L in cats and 0.6 mmol/L in dogs are considered to be ionized hypermagnesemia.[7]

57.4.4 Therapy

Therapy consists first and foremost of stopping all exogenous magnesium administration. Further treatment is based on the degree of hypermagnesemia, clinical signs, and renal function. A patient with mild clinical signs such as depression and hyporeflexia can be treated with supportive care and observation, provided that renal function is normal. More severe cases that involve unresponsiveness, respiratory depression, and any degree of hemodynamic instability should be treated with intravenous calcium. Calcium is a direct antagonist of magnesium at the neuromuscular junction and may be beneficial in reversing the cardiovascular effects of hypermagnesemia. Calcium gluconate can be given at 0.5 to 1.5 ml/kg as a slow intravenous bolus over 10 minutes. Saline diuresis and furosemide can also be used to accelerate renal magnesium excretion. Furosemide should not be given to a dehydrated or hypovolemic patient. In patients with severely impaired renal function, peritoneal dialysis or hemodialysis may be required if treatment is necessary.

In patients with severe clinical signs, anticholinesterases may be administered to offset the neurotoxic effects of hypermagnesemia. Physostigmine can be given at 0.02 mg/kg IV q12h until clinical signs subside. In severe cases complicated by cardiopulmonary arrest, intubation and mechanical ventilation are recommended. Hypermagnesemic shock may be refractory to epinephrine, norepinephrine, and other vasopressors, making resuscitation efforts extremely difficult.[5,22]

57.5 SUGGESTED FURTHER READING*

S Bateman: Disorders of magnesium: magnesium deficit and excess. In SP DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 3, 2006, Saunders, St. Louis, *An excellent in-depth discussion of the causes, clinical signs, diagnosis, and therapy of hypomagnesemia and hypermagnesemia.*

N Dhupa: Magnesium therapy. In JD Bonagura (Ed.): *Kirk's current veterinary therapy XIII*. ed 13, 2000, Saunders, Philadelphia, *An excellent discussion on the management of hypomagnesemia in small animal patients*.

N Dhupa, J Proulx: Hypocalcemia and hypomagnesemia. *Vet Clin North Am Small Anim Pract*. **28**, 1998, 587, *An excellent review of the clinical manifestations, causes, and management of hypocalcemia and hypomagnesemia.*

PA Schenck, DJ Chew: In *Understanding recent developments in hypocalcemia and hypomagnesemia*. In Proceedings of the Twenty-third American College of Veterinary Internal Medicine Forum, Baltimore, June 1-4, 2005, *An excellent discussion of developments in hypocalcemia and hypomagnesemia.*

* See the CD-ROM for a complete list of references

58 Chapter 58 Phosphate Disorders

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58.1 KEY POINTS

- Energy-rich phosphates provide power for cell membrane pumps and ion channels to maintain electrochemical gradients and electrical currents that operate most biologic systems.
- Severe hypophosphatemia can cause hemolysis, rhabdomyolysis, impaired renal function and acid-base regulation, and impaired glucose metabolism.
- Hyperphosphatemia can cause hypocalcemia, renal secondary hyperparathyroidism, and metastatic calcification.

58.2 INTRODUCTION

Phosphorus is essential for many important biologic processes including those requiring energy from adenosine triphosphate (ATP), one of the most important substances in nature. Hyperphosphatemia and hypophosphatemia are diagnostically important as indicators of underlying disease and therapeutically important because phosphorus-directed therapy may improve patient care and outcome.

58.3 CHEMISTRY

Plasma phosphorus consists of organic (phospholipids, phosphate esters) and inorganic forms (orthophosphate, pyrophosphate). Clinical laboratories report inorganic phosphorus levels, which may be taken to be the orthophosphate fractions because the pyrophosphate amount is small. The orthophosphates are in three forms: free (55%), protein bound (10%), and complexed to magnesium or calcium (35%). The free fractions are mainly present as divalent HPO_4^{2-} or monovalent $H_2PO_4^-$ species; these ionic species are the active forms and their levels are regulated. At a pH of 7.4 they exist in a 4:1 divalent-to-monovalent ratio (i.e., 4 mmol HPO_4^{2-} to 1 mmol $H_2PO_4^-$).

Clinical laboratories report the elemental phosphorus bound in phosphate molecules in the sample as phosphorus (inorganic) in mg/dl. But it is the phosphate molecule that participates in biologic processes, usually expressed in mEq/L or mmol/L. Unit conversion reveals that 3.1 mg/dl of phosphorus = 1 mmol/L phosphate = 1.8 mEq/L phosphate.[1]

58.4 TERMS

Confusion can arise because the terms *phosphorus* (the element) and *phosphate* (the molecule) are often used interchangeably. For simplicity in this chapter, the term *phosphate* is used to mean either phosphorus or phosphate.

58.5 DISTRIBUTION AND FUNCTION

Total body phosphate is distributed as follows: 85% hydroxyapatite in bone (a complex of calcium, phosphate, and hydroxyl ions), 15% in soft tissue, and less than 1% in the extracellular compartment. Phosphate has an important structural and functional role, essential to many biologic processes. For example, phosphate-dependent energy systems are responsible for the maintenance of electrochemical gradients across cell membranes, for the generation of electrical currents, and for driving muscle contractions. Phosphate is also involved in protein function regulation; it is a component of deoxyribonucleic acid and ribonucleic acid, and it is essential to the structure of bone and teeth in addition to having acid-base effects.

58.6 HOMEOSTASIS

Phosphate homeostasis is maintained by intestinal absorption of phosphate balanced by renal regulation of serum phosphate concentration, [P]. Phosphate is conserved by renal reabsorption, decreases in fecal excretion, and growth cessation. Phosphate exchange between extracellular and soft tissue or bone compartments plays a role in metabolism but is not primarily involved in homeostasis. Phosphate homeostasis is affected by parathyroid hormone (PTH), vitamin D, and calcitonin, but can occur without hormonal influence.[1]

58.6.1 Intestinal

Dietary phosphate is absorbed in the small intestine passively and by vitamin D–dependent transport. Passive transport is by diffusional flux through the paracellular pathway and is the most important means of absorption. Factors promoting intestinal absorption are sodium stimulation of a 1,25-(OH)2vitD (calcitriol)–sensitive apical sodium-phosphate cotransporter, decreasing pH, and growth hormone. If luminal phosphate is in short supply, because of either low dietary phosphate or the presence of phosphate-binding drugs, vitamin D–dependent active transport becomes important. Hyperphosphatemia regulates vitamin D metabolism by stimulating production of an inactive form of vitamin D, thus decreasing active vitamin D and therefore decreasing intestinal phosphate absorption.

58.6.2 Renal

Phosphate is reabsorbed in the proximal tubule by a transcellular sodium-phosphate symporter on the apical side 244 and a phosphate anion antiporter on the basolateral side of the renal epithelial cells. When maximal tubular 245 reabsorption of phosphate (TmP) is reached, the rest is excreted in the urine. This is the set point for serum [P]. The normal filtered load of phosphate is just a little higher than the TmP so that a small amount spills in to the urine. Tubular reabsorption is decreased by diuresis. Growth hormone increases TmP so that reabsorption is increased. This is the likely mechanism of increased serum [P] in young animals.

The three most important hormones affecting renal handling of phosphate are PTH, calcitriol, and calcitonin, although regulation of phosphate can be maintained without them. The effect of PTH is to decrease renal reabsorption of phosphate by inhibiting the sodium-phosphate symporter while increasing reabsorption of calcium. Calcitriol plays a small role in phospate reabsorption, mostly by its primary effect of decreasing PTH. Calcitonin has a hypophosphatemic effect (see Bone, next).

58.6.3 Bone

Acutely, PTH promotes transfer of calcium, but not phosphate, from the soluble part of bone where ions cross the membrane barrier created by osteoblasts and osteocytes. In stable bone, PTH stimulates increased osteoclastic and decreased osteoblastic activity, resulting in release of calcium and phosphate. In spite of the increased release of phosphate from bone to the extracellular fluid, the phosphaturic effect of PTH prevents hyperphosphatemia if renal function is normal.

Calcitonin's hypophosphatemic effect is attributable to inhibition of bone resorption (by inhibiting osteoclasts) and promoting movement of phosphate from extracellular fluid into bone.

58.7 SERUM PHOSPHATE CONCENTRATION

Normal values for [P] are approximately 3 to 6 mg/dl in adult dogs and cats.[2] In young dogs and cats [P] is significantly higher than in adults. Values for [P] as high as 11 mg/dl are normal in growing puppies.[3] In kittens from birth to 8 weeks, a reference interval of 7 to 11 mg/dl was determined.[4] Values decrease to adult levels by 12 months of age. Interpretation of [P] should be made with awareness that serum levels may not parallel intracellular stores, because phosphate is mostly intracellular. Diurnal variation in [P] has been observed in dogs with concentrations lowest in morning, highest at midnight.[1]

Autoanalyzers dependent on a color reaction for phosphate analysis may produce falsely increased values because of the turbidity caused by proteins in hyperglobulinemic patients.[5] Hyperlipidemia may cause a false increase, and in vitro hemolysis may cause release of intracellular phosphate. A falsely low value may be found in samples containing mannitol, because it binds the molybdate used in the colorimetric assay in some analyzers. Conjugated bilirubin may increase or decrease the [P] value depending on the assay used.

58.8 HYPOPHOSPHATEMIA

58.8.1 Definition

Hypophosphatemia refers to a decrease in [P] below the normal range. Values of concern are those less than 2 mg/dl. Phosphate-deficient diets or depletion of phosphate body stores are not always reflected in decreases in [P]. In phosphate deprivation there is no net loss from the body. In starvation, which is caloric deprivation, phosphate is lost proportionately to other cellular elements so that the phosphate content of the remaining cells is normal.

58.8.1.1 Box 58-1 Causes of Hypophosphatemia or Phosphate Depletion

58.8.1.1.1 Decreased Intestinal Absorption or Increased Loss

Phosphate-binding drugs

Omission of phosphate from diet

Vomiting, diarrhea

Malabsorption

Vitamin D deficiency

58.8.1.1.2 Redistribution From Extracellular Fluid to Cells and Bone

Intravenous glucose, high insulin levels (exogenous, endogenous)

Diabetes mellitus, diabetic ketoacidosis

Hyperalimentation (refeeding syndrome)

Hepatic lipidosis

Respiratory alkalosis

Metabolic acidosis

Epinephrine

Salicylate poisoning

Resynthesis of bone

58.8.1.1.3 Renal or Dialysis-Associated Loss

Diuresis

Diuretic drugs (furosemide, mannitol, thiazides, acetazolamide)

Diabetes mellitus, diabetic ketoacidosis

Hypomagnesemia

Hyperparathyroidism

Dialysis with phosphate-deficient dialysate

Malignancy

Renal tubular defects (Fanconi syndrome)

58.8.2 Causes

Three mechanisms of hypophosphatemia or phosphate depletion are decreased intestinal absorption, redistribution of phosphate from extracellular to intracellular sites, and renal (or dialysis-associated) loss (Box 58-1).

58.8.2.1 Decreased Intestinal Absorption

Phosphate-binding antacids decrease intestinal absorption of phosphate from dietary and secreted sources. Gastrointestinal disease can interfere with phosphate absorption because of vomiting, diarrhea, or malabsorption. Vitamin D–dependent phosphate absorption is important in states of low dietary phosphate or in the presence of phosphate-binding drugs, and its deficiency may cause hypophosphatemia.

58.8.2.2 Redistribution

Shift of phosphate from the extracellular compartment into cells and bone may result in decreased [P] with or without decrease in body stores.

58.8.2.2.1 Insulin and Glucose

Intravenous administration of glucose-containing solutions or high insulin levels (exogenous or endogenous) promotes movement of phosphate and glucose into cells where phosphate is trapped as glucose-6-phosphate.

58.8.2.2.2 Refeeding

Hyperalimentation promotes cell growth and repletion of cellular phosphate stores. If feeding solutions are insufficiently supplemented with phosphate, significant hypophosphatemia can result.[6,7] In cats with hepatic lipidosis, hypophosphatemia most commonly occurs with refeeding.

58.8.2.2.3 Acid-Base

Alkaline intracellular pH stimulates phosphofructokinase and therefore glycolysis, which draws phosphate into the cells to form phosphate-containing intermediate molecules, an effect that has been shown in hyperventilated dogs. Low phosphate can occur as a result.

Acidic intracellular pH promotes degradation of phosphate-containing intracellular compounds, causing release of phosphate. This would be expected to cause hyperphosphatemia, but subsequent phosphaturia is promoted because acidosis impairs the sodium-phosphate transporter on the renal tubular epithelial cell. The net result may be hypophosphatemia.

58.8.2.2.4 Epinephrine

Epinephrine mediates redistribution of phosphate out of the extracellular compartment. This response occurs at about the same epinephrine levels as do the chronotropic and pressor responses. Conditions promoting a rise in epinephrine, such as sepsis, burn injury, strenuous exercise, or administration of exogenous epinephrine, may cause acute hypophosphatemia.

58.8.2.3 Renal or Dialysis-Associated Loss

Diuresis (saline, drug-induced, osmotic) augments phosphaturia. Hypomagnesemia augments phosphaturia, but it rarely causes hypophosphatemia alone. Hyperparathyroidism promotes hypophosphatemia by increasing PTH which has a phosphaturic effect.[8] Hyperparathyroidism may be primary or secondary to renal disease or an all-meat (low calcium) diet in carnivores. Renal tubular defects such as Fanconi syndrome may promote phosphaturia. They have a variable effect on [P]. Some malignancies promote phosphaturia, because they produce substances that decrease renal phosphate absorption and renal hydroxylation of vitamin D. Hypercalcemia of malignancy often is associated with hypophosphatemia.

58.8.2.4 Mixed Causes

Uncontrolled diabetes mellitus, diabetic ketoacidosis, and hyperglycemic hyperosmolar nonketotic syndrome cause phosphaturia and, combined with inadequate dietary intake, result in loss of body stores of phosphate.[9] Mechanisms include osmotic diuresis, metabolic acidosis, and insulin therapy.

Salicylate poisoning may cause respiratory alkalosis and may also directly stimulate glycolysis, either of which draws phosphate into the cells.

Eclampsia is due to a failure to mobilize calcium and phosphate from bone to match losses in milk.

Hypercalcemia of malignancy often is associated with hypophosphatemia.

58.8.3 Effects

If hypophosphatemia is severe enough to cause a significant decrease in phosphate-containing metabolites, it can cause abnormal function of many organs and systems.

58.8.3.1 Cell Function

Phosphate-depleted red blood cells have impaired release of oxygen because of decreases in 2,3-diphosphoglycerate, abnormal shape and deformability, and are at risk for hemolysis caused by ATP depletion.[10,11] Hemolysis can occur at [P] values less than 1 mg/dl in dogs and has been reported at less than

2.5 mg/dl in cats.[7] Phosphate depletion impairs white blood cell chemotaxis, phagocytosis, and bactericidal activity. Impaired clot retraction and shortened platelet life span with a tendency toward hemorrhage occurs in dogs.[6]

58.8.3.2 Muscle

The myopathy of phosphate depletion is caused by a decreased capacity to form ATP. Clinical signs include weakness, myocardial insufficiency, and respiratory insufficiency. Rhabdomyolysis may result, especially in dogs with earlier subclinical phosphate depletion.[12]

58.8.3.3 Metabolic

Impaired glucose metabolism, phospholipid synthesis, and bone mineralization, as well as increased release of magnesium from bone and decreased reabsorption in the kidney, and liver dysfunction may result from severe hypophosphatemia.[13]

58.8.3.4 Acid-Base

Phosphate depletion can cause renal proximal tubular bicarbonate wasting, impair distal acidification, and decrease ammoniagenesis, resulting in metabolic acidosis.

58.8.4 Therapy

It is difficult to identify a specific benefit from treatment of hypophosphatemia, because simultaneous treatment of acid-base, electrolyte, and nutritional abnormalities impairs evaluation of the effect of phosphate repletion alone. When phosphate levels are less than 1 mg/dl, complications such as hemolysis, respiratory failure, muscle weakness, and impaired oxygen delivery may occur.[10] Phosphate levels less than 2 mg/dl have been associated with muscle weakness, anorexia, or tremor in human patients.[13] Phosphate levels less than 1.5 mg/dl should be treated in diabetic cats.[10] Because diabetic ketoacidosis is a common cause of hypophosphatemia, and because of the deleterious effects of hypophosphatemia, some authors recommend the routine administration of phosphate to these patients unless they are hyperphosphatemic.[13]

58.8.4.1 Prevention

Phosphate-binding drugs, intravenous glucose, and diuretics should be stopped, if possible. Feeding solutions, especially in debilitated patients, should be supplemented with phosphate.

58.8.4.2 Treatment

Because [P] may not parallel total body stores, therapy must be monitored closely to avoid hyperphosphatemia and other adverse effects (see next section). Phosphate preparations are available for delivery by oral and intravenous routes. For mild hypophosphatemia, oral is the route of choice. Skim milk has 1 g of calcium and phosphate per quart and may be enough in mild hypophosphatemia.[14] Phosphate preparations for oral use are available. Enteral phosphate can cause diarrhea. 246 247

58.8.4.2.1

Box 58-2 Precautions Required for Intravenous Phosphate Supplementation

- Check phosphate level q6-12h. Discontinue IV supplementation when [P] is >2 mg/dl.
- If using potassium phosphate, be sure that the rate does not exceed the maximum potassium infusion rate.
- If the patient is hypercalcemic or hypocalcemic, administer phosphate at a slower rate and monitor calcium levels.
- If the patient is hypomagnesemic, concurrent magnesium supplementation is suggested.
- Phosphate solutions for intravenous use are hyperosmolar and should be diluted before administration.
- Hypotension, hypomagnesemia, and hyperosmolality may result from intravenous administration of phosphate, especially if administered too rapidly.
- Do not add calcium to phosphate preparations. Precipitation can result.

In moderate to severe hypophosphatemia, intravenous supplementation is indicated. Preparations for intravenous use include potassium phosphate (93 mg/ml phosphate + 4 mEq/ml potassium) and sodium phosphate (93 mg/ml phosphate + 4 mEq/ml sodium). Suggested dosages are 0.011 to 0.033 mmol/kg/hr of phosphate. When [P] is greater than 2 mg/dl the infusion should be discontinued. For patients with severe diabetes mellitus, a 50:50 mixture of potassium chloride and potassium phosphate at a rate not to exceed the maximum for potassium infusion (0.5 mEq/kg/hr) is useful.[15] Cats with hepatic lipidosis can become hypophosphatemic, especially when refeeding is started, and supplementation as for the diabetic may be needed. Several important precautions should be taken with all intravenous phosphate supplementation; these are listed in Box 58-2.

58.9

HYPERPHOSPHATEMIA

58.9.1

Causes

Hyperphosphatemia occurs by three mechanisms: increased phosphate load (exogenous or endogenous), decreased glomerular filtration rate, and increased renal tubular absorption. The most common cause is renal failure (Box 58-3).

58.9.1.1

Increased Phosphate Load

Rapid introduction of large amounts of phosphate orally or intravenously, when the kidney is set to reabsorb nearly all filtered phosphate, can result in hyperphosphatemia.[16] Although the large intestine usually absorbs little phosphate, enemas containing phosphate can cause hyperphosphatemia,[17] especially if there are mucosal defects. Vitamin D intoxication causes increased intestinal absorption and increased bone resorption. Hyperphosphatemia was reported with intoxication by calcipotriene, an antipsoriasis drug causing hypercalcemia, and with liposome-encapsulated amphotericin B.[18,19]

58.9.1.2

Redistribution

Phosphate may be released from intracellular stores in bone resorption, or processes causing cell damage such as necrosis, tumor lysis syndrome,[20] rhabdomyolysis, or hemolysis. Metabolic or respiratory acidosis, strenuous exercise, and malignant hyperthermia cause a decrease in intracellular pH, which inhibits glycolysis, thus decreasing incorporation of inorganic phosphate into organic compounds. This increases the intracellular free phosphate, which then distributes to the extracellular compartment.[21]

58.9.1.2.1

Box 58-3 Causes of Hyperphosphatemia

58.9.1.2.1.1

Increased Phosphate Load

58.9.1.2.1.1.1

Exogenous

Large amount of oral phosphate or IV phosphate introduced rapidly

Phosphate-containing enemas

Vitamin D intoxication, cholecalciferol rodenticide toxicity

Drugs (calcipotriene, liposomal amphotericin B)

58.9.1.2.1.1.2

Endogenous (Redistribution)

Bone

Necrosis

Metabolic acidosis, especially organic acidosis

Acute respiratory acidosis

Tumor lysis syndrome

Acute hemolysis

Rhabdomyolysis

Strenuous exercise

Malignant hyperthermia

58.9.1.2.1.2 Decreased Renal Excretion

Renal failure (prerenal, renal, post)

Urinary tract rupture

58.9.1.2.1.3 Increased Renal Reabsorption

Hypoparathyroidism

Acromegaly

Hyperthyroidism

Glucocorticoid withdrawal

Bisphosphonates

58.9.1.3 Decreased Glomerular Filtration Rate

The most common cause of hyperphosphatemia is renal failure. In acute failure, phosphate often rises before creatinine and blood urea nitrogen. In chronic failure, phosphate rises after adaptive mechanisms such as increased PTH, decreased calcitriol, and intrinsic tubular adaption have failed.

58.9.1.4 Increased Renal Absorption

Various endocrine abnormalities promote hyperphosphatemia. In hypoparathyroidism, the phosphaturic action of PTH is diminished.[22] Growth hormone excess in acromegaly or hyperthyroidism increases the TmP and glomerular filtration rate. Hyperthyroidism also causes increased bone resorption and PTH suppression.[16] Glucocorticoids inhibit sodium-dependent phosphate uptake in the kidney, and their withdrawal can cause hyperphosphatemia.

Bisphosphonates, used to treat hypercalcemia, can decrease phosphate excretion and cause hyperphosphatemia.

58.9.2 Effects

58.9.2.1 Hypocalcemia

Hyperphosphatemia, especially if it develops rapidly (within a few days), may cause a clinically significant ionized hypocalcemia, possibly severe enough to cause tetany. The mechanism is calcium precipitation, inhibition of bone resorption, and suppression of renal hydroxylation of vitamin D.[13] In renal failure, the hyperphosphatemia-induced decrease in serum calcium stimulates PTH and plays a role in renal secondary hyperparathyroidism.

58.9.2.2 Renal

Hyperphosphatemia from any cause can promote renal intratubular precipitation of calcium and phosphate, which has the potential to interfere with tubular function and worsen the hyperphosphatemia.

58.9.2.3 Metastatic Calcification

Deposition of calcium phosphate salts in undamaged soft tissue caused by elevated calcium-phosphate product (Ca × P) is one form of metastatic calcification. The level of Ca × P at which this is likely to occur, previously reported at 70 mg^2/dl^2 has been reevaluated and a therapeutic goal in human patients with renal failure of 55 mg^2/dl^2 suggested.[21] The mineral deposits incite a periarticular, articular, and conjunctival inflammatory response in humans. Calcium-phosphate deposits also occur in the heart and lungs, but their deposition is not as clearly related to an increased Ca × P.[22] Calciphylaxis, a medium and small artery vasculopathy with mural calcification, is associated with an increased Ca × P. The syndrome results in ischemia and necrosis of skin, fat, organs, and skeletal muscle.[23] In dogs and cats with chronic renal failure, metastatic calcification is identified but does not usually cause clinical signs. Control of hyperphosphatemia is important in the management of renal secondary hyperparathyroidism.[24]

58.9.2.4 Acid-Base

Phosphate is a weak acid at physiologic pH; hence, increases in [P] will cause a metabolic acidosis.[25]

58.9.3 Therapy

58.9.3.1 Prevention

Exogenous sources of phosphate and intestinal absorption of phosphate should be reduced in patients with renal impairment. Endogenous sources of phosphate from cell breakdown, as in tumor lysis syndrome, should be managed with renal support and avoidance of nephrotoxic agents.

58.9.3.2 Treatment

Volume expansion and diuresis promote renal phosphate excretion. Phosphate is removed during dialysis at a rate determined by the volume and composition of the dialysate and the body fluids, and by the type of dialysis membrane used.

Aluminum-containing phosphate-binding drugs (aluminum hydroxide, aluminum carbonate, and aluminum oxide) bind intestinal phosphate so that dietary and secreted phosphate are not absorbed. They also decrease absorption of endogenous phosphate excreted from parotid glands and the pancreas.[25] Use of aluminum-containing phosphate binders in human patients has declined because of toxicity, but there is little evidence of toxicity in dogs and cats. Calcium carbonate and calcium acetate are available and are widely prescribed in human patients, but they may promote hypercalcemia.[26] Non–calcium-containing phosphate binders, such as sevelamer hydrochloride, are in use in humans and animals.[25,27]

58.10 SUGGESTED FURTHER READING*

EC Feldman, B Hoar, R Pollard, RW Nelson: Pretreatment clinical and laboratory findings in dogs with primary hyperparathyroidism: 210 cases (1987–2004). *J Am Vet Med Assoc*. **227**, 2005, 756, *The best description of abnormalities found in dogs with hyperparathyroidism*.

U Giger: Regenerative anemias caused by blood loss or hemolysis. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, St Louis, *An excellent book chapter in which hemolysis secondary to hypophosphatemia is reviewed and guidelines for phosphate therapy are provided.*

RW Nelson, GH Turnwald, MD Willard: Endocrine, metabolic, and lipid disorders. In MD Willard, H Tvedten, GH Turnwald (Eds.): *Small animal clinical diagnosis by laboratory methods*. ed 4, 2004, Saunders, Philadelphia, *One of the best of the clinical pathology handbooks*.

M Schaer: Iatrogenic hyperphosphatemia, hypocalcemia and hypernatremia in a cat [adverse reaction to phosphate enema]. *J Am Anim Hosp Assoc*. **13**, 1977, 39, *Case report that highlights the risk of phosphate-containing enema solutions*.

* See the CD-ROM for a complete list of references

59 Chapter 59 Acid-Base Disturbances

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59.1 KEY POINTS

- The Henderson-Hasselbalch and strong ion approaches to acid-base analysis group parameters that the clinician would prefer to separate to isolate cause and effect and to guide treatment.
- Respiratory changes in acid-base are caused by changes in the plasma carbon (CO_2) dioxide concentration. This is a measure of ventilation and its ability to match cellular production of CO_2.
- Metabolic changes can be divided into changes related to sodium, chloride, protein, phosphate, and lactate, as well as the many strong anions that are not routinely quantified for acid-base effect but can play a major role in acidemia in disease states.
- A base excess algorithm that estimates the contribution of each of the metabolic contributors to an acid-base disturbance is a practical method to identify the contribution of each mediator and to make more accurate decisions for therapy.

59.2 INTRODUCTION

Changes in hydrogen ion concentration in the body are associated with molecular changes that can have significant physiologic effects. Consequently, homeostasis aims to maintain a normal hydrogen ion concentration. Hydrogen ion concentration is measured as pH, the negative base-10 logarithm of the hydrogen ion concentration, $[H^+]$. The normal extracellular pH is generally in the range of 7.4. Elevated blood hydrogen ion levels (pH <7.4) are described as an *acidemia,* and reduced hydrogen ion levels (pH >7.4) are described as an *alkalemia.* [1]

There is a widely held misunderstanding that the body regulates hydrogen ion concentration within very narrow limits. This is a result of the observation that normal pH is approximately 7.41 in dogs and 7.39 in cats and that changes in pH become life threatening if pH falls below 7.1 or rises above 7.7. The misconception that this represents exquisite control of $[H^+]$ is a result of the logarithmic nature of the pH scale. In reality, the life-threatening alarm values for pH represent a $[H^+]$ that ranges from 80 nanoEq/L at a pH of 7.1 to 20 nanoEq/L at a pH of 7.7. This is a four-fold difference in $[H^+]$ between the low and high alarm values. This is equivalent to the statement that sodium concentration is well regulated because its concentration must fall below 75 mEq/L or rise above 300 mEq/L before we become alarmed. Clearly sodium is regulated much more closely, and as clinicians we are alarmed well before the concentration reaches these extremes.

Several approaches to acid-base analysis have been developed. They include the Henderson-Hasselbalch, or conventional, approach that uses pH, partial pressure of carbon dioxide (PCO_2), bicarbonate (HCO_3^- , base excess (BE), and anion gap, and the Stewart approach, which uses pH, PCO_2, strong ion difference (SID), and the quantity of weak acids (A_{TOT}). As clinicians, we find ourselves naming acid-base disturbances while gaining little understanding of the etiology of the patient's acid-base problems and little insight into effective therapy. The primary problem is that within each of these traditional approaches multiple etiologic factors are grouped together.

The clinician needs a way to isolate cause and effect to assess the mechanisms behind the disturbance and to focus treatment.

59.2.1 Box 59-1 Henderson-Hasselbalch Equation

$$pH = 6.1 + \log\left(\left[HCO_3^-\right] \div \left[0.03 \times PCO_2\right]\right)$$

where 6.1 is the pKa in body fluids; $[HCO_3^-]$ is the concentration of HCO_3^- measured in mmol/L; 0.03 is the solubility coefficient for carbon dioxide in plasma; and PCO_2 is the partial pressure of carbon dioxide in mm Hg.

Both approaches to acid-base analysis start with a measurement of pH, a parameter that represents the chemical summation of all acid-base disturbances. An abnormal pH is interpreted as acidemia or alkalemia. This is the net change in $[H^+]$ that results from all acidifying events (acidosis) and all alkalinizing events (alkalosis). Rarely is an acidemia or alkalemia so severe that the clinician's objective is to treat the disturbance without regard to etiology. The real value in acid-base analysis is to discover the multiple compensating and counterbalancing causes that are common in critical care patients.

Acid-base disturbances are broadly categorized as respiratory or metabolic in nature. Conventional acid-base analysis is based on the Henderson-Hasselbalch equation (Box 59-1), which uses bicarbonate concentration, $[HCO_3^-]$, as the sole measure of the metabolic contribution to acid-base balance and the PCO_2 as the single causative agent for respiratory acid-base disturbances. Using this conventional approach the primary abnormality (metabolic or respiratory) is the system that is responsible for the initial change in pH. For example, an acidemia with a low HCO_3^- and low PCO_2 would be considered a primary metabolic acidosis, because the acidemia must be a result of the low HCO_3^-.[1,2] The conventional approach identifies four acid-base abnormalities; these are described in Table 59-1.

The PCO_2 is universally considered the sole causative agent for respiratory acid-base disturbances. However, the parameter(s) used to assess metabolic disturbances varies with the analytic approach chosen. For clinical application, acid-base disturbances should be studied from the perspective of the individual etiologic agents that cause them (Table 59-2).

59.3 RESPIRATORY ACID-BASE DISTURBANCES

Carbon dioxide acts as an acid because of its ability to react with water to produce carbonic acid. In this way, the 249 250 PCO_2 affects the HCO_3^- buffer system and ultimately the hydrogen ion concentration.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Table 59-1 Acid-Base Disturbances Identified With the Conventional Approach

Acid-base Disturbance	**pH**	**PCO_2**	**$[HCO_3^-]$**
Respiratory acidosis	↓	↑	↑
Respiratory alkalosis	↑	↓	↓
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑

$[HCO_3^-]$, Bicarbonate concentration measured in mEq/L;

PCO_2, is partial pressure of carbon dioxide measured in mm Hg; ↑, increased; ↓, decreased.

Table 59-2 Acid-Base Disturbances Based on Etiology

Respiratory Causes of Acid-Base Disturbances	
Increased carbon dioxide	Respiratory acidosis (hypoventilation)
Decreased carbon dioxide	Respiratory alkalosis (hyperventilation)
Metabolic Causes of Acid-Base Disturbances	
Decreased sodium	Hyponatremic metabolic acidosis
Increased sodium	Hypernatremic metabolic alkalosis
Increased chloride	Hyperchloremic metabolic acidosis
Decreased chloride	Hypochloremic metabolic alkalosis
Increased protein	Hyperproteinemic metabolic acidosis
Decreased protein	Hypoproteinemic metabolic alkalosis
Increased phosphate	Hyperphosphatemic metabolic acidosis
Decreased phosphate	Hypophosphatemic metabolic alkalosis
Increased unmeasured anions	Lactic acidosis
	Ketoacidosis
	Toxic acidosis (ethylene glycol, salicylate)
	Acidosis of renal failure

Because carbon dioxide is a gas for which concentration in the blood is controlled by pulmonary ventilation, the lung plays a role in controlling acid-base status. This is a rapid process that can alter blood pH within minutes. Normal arterial PCO_2 in dogs is 37 mm Hg and in cats it is 31 mm Hg. The PCO_2 is maintained by normal pulmonary function, normal function of the diaphragm and respiratory muscles, normal pleural space dynamics, and normal respiratory drive controlled by the brain.

If the PCO_2 is abnormal, there is a respiratory component to the acid-base disturbance, but it is not necessarily pathologic. PCO_2 is determined directly by effective alveolar minute ventilation which, in turn, is controlled by the respiratory center of the brain. CO_2, oxygen, and pH can all alter alveolar minute ventilation via central and peripheral chemoreceptors. Chemoreceptors do not respond to changes in PCO_2 directly; rather they detect associated changes in $[H^+]$. Hence abnormalities in PCO_2 can be subsequent to primary respiratory disorders or can occur in response to metabolic acid-base abnormalities and their associated changes in $[H^+]$. When metabolic processes occur that increase $[H^+]$, the respiratory center will respond with hyperventilation to lower PCO_2. Conversely when $[H^+]$ is low, hypoventilation will occur to increase PCO_2 appropriately. This is the normal respiratory response to a metabolic alteration and serves to minimize the overall change in pH.[1,4]

Table 59-3 Expected Compensatory Changes to Primary Acid-Base Disorders

Primary Disorder	**Expected Compensation**
Metabolic acidosis	↓ PCO_2 of 0.7 mm Hg per 1 mEq/L decrease in $[HCO_3^-]$ ±3
Metabolic alkalosis	↑ PCO_2 of 0.7 mm Hg per 1 mEq/L decrease in $[HCO_3^-]$ ±3
Respiratory acidosis—acute	↑ $[HCO_3^-]$ of 0.15 mEq/L per 1 mm Hg ↑ PCO_2 ±2
Respiratory acidosis—chronic	↑ $[HCO_3^-]$ of 0.35 mEq/L per 1 mm Hg ↑ PCO_2 ±2
Respiratory alkalosis—acute	↓ $[HCO_3^-]$ of 0.25 mEq/L per 1 mm Hg ↓ PCO_2 ±2
Respiratory alkalosis—chronic	↓ $[HCO_3^-]$ of 0.55 mEq/L per 1 mm Hg ↓ PCO_2 ±2

$[HCO_3^-]$, Bicarbonate concentration measured in mEq/L; *PCO_2*, partial pressure of carbon dioxide measured in mm Hg, ↑, increased; ↓, decreased.

Conventional acid-base nomenclature states that a metabolic disturbance that is accompanied by an appropriate compensatory respiratory change is classified as a simple metabolic disturbance and the respiratory component is not named. A compensatory change is considered “appropriate” if it is of a magnitude similar to that predicted by the calculated compensatory response. These calculations are provided in Table 59-3 and are discussed further later in this chapter.[1,3]

In clinical practice it may be beneficial to identify the respiratory component, because this physiologic response may have more serious consequences for the patient than the initial metabolic disturbance. For example, a patient in shock with serious head trauma may present with a metabolic acidosis and appropriate respiratory compensation. Although the respiratory alkalosis in this case is compensatory and not considered an acid-base abnormality, it may be clinically significant because the low PCO_2 causes cerebral vasoconstriction, which may be dangerous in this patient. Further assessment, including clinical monitoring, will identify if the respiratory change is likely to be physiologic or if there are other, pathologic, respiratory disturbances that may amplify or attenuate the physiologic response.

59.3.1 Increased Carbon Dioxide: Respiratory Acidosis

Respiratory acidosis may result from a primary respiratory disorder or it can be a physiologic respiratory compensation for a metabolic alkalosis. An increase in HCO_3^- of 1 mEq/L should result in an increase in PCO_2 of 0.7 mm Hg in both dogs and cats.[1,3]

Pathologic respiratory acidosis results from an imbalance in CO_2 production via metabolism and excretion via the lung. Common causes include large airway obstruction or generalized small airway obstruction such as asthma, respiratory center depression, neuromuscular disease, heat stroke, malignant hyperthermia, pleural space disease, and chest wall disruption.[4] The result is respiratory failure and hypoventilation. Cardiopulmonary arrest is a special case in which CO_2 accumulates in tissues as perfusion and ventilation ceases. Initiation of spontaneous or mechanical breathing may provide minute volumes normally associated with hyperventilation, but the plasma CO_2 levels will remain high until effective circulation is established and excess CO_2 dioxide is eliminated.

Therapy for pathologic respiratory acidosis involves improving ventilation by treating the underlying cause. In severe cases of hypoventilation that persists despite therapy, mechanical ventilation is indicated (see Chapter 213, Basic Mechanical Ventilation). Elevated levels of CO_2 can cause hypoxemia in patients breathing room air, and all animals with significant hypercapnia (>60 mm Hg) should receive oxygen therapy.[4]

59.3.2 Decreased Carbon Dioxide: Respiratory Alkalosis

Respiratory alkalosis may result from pulmonary or nonpulmonary disease processes causing hyperventilation, or it can be a physiologic respiratory compensation for metabolic acidosis. A decrease in HCO_3^- of 1 mEq/L should result in a decrease in PCO_2 of 0.7 mm Hg in dogs.[3] In cats, limited evidence suggests that the PCO_2 does not change, and this calculation for expected compensation is not recommended.

Pathologic respiratory alkaloses usually are caused by hypoxemia that stimulates chemoreceptors, pulmonary disease that stimulates stretch receptors and nociceptors independent of hypoxemia, heart failure and baroreceptor stimulation, pain and anxiety, excessive mechanical ventilation, and multiple factors that stimulate centrally mediated hyperventilation.[4]

Therapy is directed at the underlying cause and at suppressing the hyperventilation if the CO_2 is less than 20 to 25 mm Hg when cerebral vasoconstriction is a concern.

59.4 METABOLIC ACID-BASE DISTURBANCES

Clinically, several measures have been used to evaluate the metabolic contribution to acid-base balance. These include HCO_3^-, BE, total carbon dioxide concentration (TCO_2), and evaluation of SID and A_{TOT}. The HCO_3^- is a calculated value provided by the blood gas machine and is the summation of many metabolic processes that can alter $[H^+]$. The HCO_3^- may hide serious but canceling acidoses and alkaloses such that the clinician has little information for effective treatment. In addition, HCO_3^- will change with changes in PCO_2; consequently, it may not be an accurate reflection of the metabolic component when there are significant respiratory acid-base abnormalities.

The BE is an alternative measure of the metabolic component. The BE provides a measure of the metabolic component that is independent of changes in PCO_2. Standardized BE equals the amount of strong acid or base needed to restore the plasma pH of 1 L of blood to 7.4 at a $PaCO_2$ of 40 mm Hg and a temperature of 37° C; it is also calculated via formulas programmed into the blood gas machine.[1] TCO_2 concentration is a result provided on serum biochemistry analyses and is a measure of the sum of HCO_3^-, carbonic acid, and the dissolved CO_2 in the system. Because HCO_3^- is quantitatively by far the major contributor to TCO_2 concentration, this measure can be used as an index of HCO_3^- levels in the absence of a blood gas result, although this value will always be slightly above the true HCO_3^- concentration. A decrease in HCO_3^-, a negative BE, and a decreased TCO_2 all indicate a metabolic acidosis, and an increase in HCO_3^-, positive BE, and increased TCO_2 are indicative of a metabolic alkalosis.

59.4.1 Box 59-2 Anion Gap Equation

$$\text{Anion gap}^{*} = \left(\left[Na^+\right] + \left[K^+\right]\right) - \left(\left[HCO_3^-\right] + \left[Cl^-\right]\right)$$

*In reality there is no actual anion gap; rather, this is a measure of unmeasured anions and cations in the system. An increase in the anion gap usually reflects an increase in unmeasured anions.

59.4.2 Anion Gap

By calculation of the anion gap, metabolic acidosis can be divided into one of two broad categories—elevated anion gap metabolic acidosis and normal anion gap metabolic acidosis.[1] When acidosis occurs without changing the anion gap, the cause is hyperchloremia (the measured chloride increases along with the acidosis so the gap does not change). Thus a normal anion gap is called *hyperchloremic acidosis* and a high anion gap is called *normochloremic acidosis*. Electroneutrality dictates that the total number of cations in the system must equal the total number of anions, so there is no anion gap in reality.

In the clinical setting, a greater proportion of cations can be measured directly in comparison with anions. The difference between the two, the anion gap, is a measure of the quantity of unmeasured anions in the system. The anion gap is calculated via the formula provided in Box 59-2. Elevations in anion gap are associated with specific disease states and may help narrow the rule-out list for the patient with metabolic acidosis (see Table 59-2). In the normal animal the unmeasured anions represented by the anion gap comprise mainly albumin and a small amount of inorganic phosphate. States of hypoalbuminemia and hyperalbuminemia alter the anion gap significantly such that it is no longer a reliable indicator of the presence of abnormal acids.[5]

59.4.3 Stewart Approach

In recognizing that multiple metabolic processes can contribute to the overall metabolic component, the Stewart approach to acid-base analysis may be more useful to the clinician. Stewart identified three individual determinants of acid-base balance. These were PCO_2, SID, and A_{TOT}.[2,6-8] SID commonly is estimated from the difference in serum sodium and chloride concentrations. According to this approach to acid-base analysis, pH is a product of water dissociation which, in turn, is determined by the balance between strong cations and anions (SID) and the presence of weak acids in the system. The relative concentration of HCO_3^- is not considered to be a determinant of pH. Increases in SID are indicative of an alkalotic effect on the system, and decreases in SID are indicative of an acidotic effect. A_{TOT} is the quantity of weak acids and consists primarily of albumin and phosphate. The interested reader is directed to references 6 through 8 for further discussion of the principles of the Stewart approach to acid-base analysis. There are still inherent problems with this system, because the calculation of SID groups the sodium and chloride effects, and A_{TOT} sums the effect of protein and phosphate.

59.4.4 Quantitative Analysis of Base Excess

Clinically it is beneficial to consider the contribution of each individual process to the overall BE to determine the cause of metabolic acid-base abnormalities, their relative magnitude, and to guide therapy. These processes include changes in sodium concentration, chloride concentration, serum protein, phosphate, lactate, and unmeasured anions. Unfortunately the mechanism by which each of these processes affects acid-base balance remains controversial. Two schools of thought are presented in this discussion; however, by using simple equations the clinician can approximate the relative impact of each of these factors on acid-base balance.[6,9]

59.4.4.1 Hyponatremic Metabolic Acidosis

Sodium is the major extracellular cation. It acts as a strong ion, so it exists in the ionic, charged form at physiologic pH. Because water follows sodium, hyponatremia can also be considered a relative increase in free water. One explanation for the acid-base effect of hyponatremia is that free water is acidic relative to normal body pH, so increases in free water (decreases in sodium) content will have an acidifying effect on the system.[10] The Stewart explanation is that if the sodium level of plasma decreases, the decrease in positive charge is offset by an increase in $[H^+]$ and a decrease in HCO_3^-. This is acidifying.

The contribution of a decrease in plasma sodium concentration is to decrease the BE (making it more negative) by 25% of the change in the patient's sodium for dogs, 22% for cats[6]:

$$\Delta\ \mathrm{BE} = 0.25 \times ([\text{Patient sodium}] - [\text{Normal sodium}]) \text{ for dogs}$$

$$\Delta\ \mathrm{BE} = 0.22 \times ([\text{Patient sodium}] - [\text{Normal sodium}]) \text{ for cats}$$

Hyponatremia is associated with sodium loss from vomiting or diarrhea, third space sodium loss, nephrotic syndrome, hypoadrenocorticism, congestive heart failure, psychogenic polydipsia, diuretic administration, hypotonic fluid use, and the syndrome of inappropriate antidiuretic hormone (SIADH) release.[1]

Treatment is directed at correcting the underlying cause and providing sodium replacement (if indicated) using appropriate replacement fluids and sodium bicarbonate. Care should be taken that fluids do not contain excess chloride, which may create a hyperchloremic metabolic acidosis and exacerbate the problem.

59.4.4.2 Hypernatremic Metabolic Alkalosis

Hypernatremia is a reflection of an alkalinizing effect on the system as described earlier. The contribution of an increase in plasma sodium concentration is to increase the BE by 25% of the change in the patient's sodium for dogs, 22% for cats[6]:

$$\Delta\ \text{BE} = 0.25 \times ([\text{Patient sodium}] - [\text{Normal sodium}]) \text{ for dogs}$$

$$\Delta\ \text{BE} = 0.22 \times ([\text{Patient sodium}] - [\text{Normal sodium}]) \text{ for cats}$$

Hypernatremia can occur with vomiting, renal failure, postobstructive diuresis, diabetes insipidus, water deprivation, sodium bicarbonate administration, use of other medications complexed with sodium, and hypertonic fluid use.

Treatment is directed at correcting the underlying cause and limiting sodium intake if elevations in sodium and osmolality are severe.

59.4.4.3 Hyperchloremic Metabolic Acidosis

Hyperchloremia is associated with an acidifying effect on the system. Chloride concentration may change independently of sodium, but it will also be altered by changes in free water in a manner parallel with sodium concentration. The free water–associated changes and their influence on acid-base status are calculated in the sodium equation. Therefore, to isolate independent changes in chloride, the measured chloride concentration must be corrected for this free water change.[1,6,9]

$$\text{Corrected chloride} = \text{Patient chloride} \times ([\text{Normal sodium}] \div [\text{Patient sodium}])$$

The conventional explanation for the acid-base effect marked by changes in chloride concentration is that it is a reflection of changes in HCO_3^- concentration. Because the two major anions in the body, chloride and HCO_3^-, are handled in a reciprocal manner, changes in HCO_3^- will be reflected by a similar but inverse change in chloride.[11] The Stewart explanation is that chloride is the major extracellular anion and as a strong ion exists in its ionic form. If the chloride level of plasma increases, the increase in negative charge is offset by an increase in $[H^+]$ and a decrease in HCO_3^-. This is acidifying.

The contribution to metabolic acid-base balance marked by an increase in plasma corrected chloride concentration is to directly decrease the BE[6,9]:

$$\Delta\ \text{BE} = ([\text{Normal chloride}] - [\text{Patients corrected chloride}])$$

Hyperchloremia may result from renal failure, diarrhea, total parenteral nutrition, and the administration of drugs or fluids that have a lower sodium-to-chloride ratio than normal. The normal sodium-to-chloride ratio is approximately 3:2.

Iatrogenic hyperchloremic metabolic acidosis is a common finding in intensive care patients receiving fluids and multiple medications. If the clinician does not pay attention to the sodium-to-chloride ratio of intravenous fluids and to the use of potassium chloride supplements and other medications that contain chloride, it is easy for it to accumulate, with serious consequences on acid-base status. Furthermore, hyperchloremic acidosis relies on the kidneys to eliminate the excess chloride, so rapid treatment is difficult and is complicated further in patients with renal tubular disease.

59.4.4.4 Hypochloremic Metabolic Alkalosis

Just as increased chloride concentrations are associated with an acidifying effect on the system, decreased 252
chloride concentrations are associated with alkalinizing effects. The contribution of a decrease in plasma 253
corrected chloride concentration is to directly increase the BE[6,9]:

$$\Delta\ \mathrm{BE} = ([\,\mathrm{Normal\ chloride}\,] - [\,\mathrm{Patient\ corrected\ chloride}\,])$$

Hypochloremia relative to sodium can occur with pyloric outflow obstruction and vomiting, diuretic administration, fluid use, or with sodium bicarbonate therapy. Treatment is directed at the underlying cause and toward restoring a normal sodium-to-chloride ratio.

59.4.4.5 Hyperproteinemic Metabolic Acidosis

Increases in serum protein are associated with an acidifying effect. The conventional explanation for this acid-base effect is that at physiologic pH plasma proteins, primarily albumin, act as weak acids. Consequently, increases in plasma protein will have an acidifying effect.[11] The Stewart explanation is that at physiologic pH proteins exert a net negative charge that in canine plasma totals about 16 mEq/L. If the protein level of plasma increases, the increase in negative charge is offset by an increase in $[H^+]$ and a decrease in HCO_3^- concentration. This is an acidifying event.

An increase in plasma proteins is unusual but may be associated with some inflammatory processes, neoplasia such as multiple myeloma, dehydration, and iatrogenic overadministration of albumin.

The contribution of an increase in total protein is to decrease the BE (more negative) by 3 times the change in the patient's total protein[6,9]:

$$\Delta\ \mathrm{BE} = 3 \times ([\,\mathrm{Normal\ protein}\,] - [\,\mathrm{Patient\ protein}\,]$$

The albumin concentration may also be substituted[6,9]:

$$\Delta\ \mathrm{BE} = 3.7 \times ([\,\mathrm{Normal\ albumin}\,] - [\,\mathrm{Patient\ albumin}\,])$$

Treatment of hyperproteinemic metabolic acidosis involves specific therapy for the underlying disease and, in extreme cases, plasmapheresis.

59.4.4.6 Hypoproteinemic Metabolic Alkalosis

Hypoproteinemia is far more common than hyperproteinemia in critically ill patients. Hypoproteinemia is associated with an alkalinizing effect on the system as discussed earlier. A decrease in plasma proteins may be caused by dilution with an increase in plasma water, loss due to vascular leak states such as protein-losing nephropathy, protein-losing enteropathy, systemic inflammation (systemic inflammatory response syndrome), or decreased synthesis due to hepatic disease or reprioritization. The result of a decrease in plasma protein is to increase the BE by 3 times the change in the patient's protein measured in g/dl[6,9]:

$$\Delta \text{ BE } = 3 \times ([\text{ Normal protein }] - [\text{ Patient protein }])$$

The albumin concentration may also be substituted[6,9]:

$$\Delta \text{ BE } = 3.7 \times ([\text{ Normal albumin }] - [\text{ Patient albumin }])$$

Treatment for hypoproteinemic metabolic alkalosis is directed at the underlying cause of the protein loss.

59.4.4.7 Hyperphosphatemic Metabolic Acidosis

Elevations in serum phosphate are associated with an acidifying effect on the system. The conventional explanation is that phosphate is a weak acid at physiologic pH; hence increases in serum phosphate concentration have an acidotic effect on the system.[11] The Stewart explanation is that the normal phosphate level of 5 mg/dl contributes approximately 2.9 mEq/L of net negative charge to plasma. An increase in negative charge from an increase in phosphate is balanced by an increase in $[H^+]$ and a decrease in HCO_3^-, an acidifying event.

The result of an increase in phosphate is to decrease the BE (more negative) by 60% of the change from normal plasma concentration of inorganic phosphorus reported in mg/dl[6,9]:

$$\Delta \text{ BE } = 0.6 \times ([\text{ Normal phosphate }] - [\text{ Patient phosphate }])$$

Hyperphosphatemia is associated with renal failure, urinary tract obstruction or disruption, cell lysis, or phosphate-containing medications such as intravenous phosphates, phosphate urinary acidifiers, and phosphate enemas. Treatment is directed at the underlying disease or removing the offending therapeutic agent. Hemodialysis and peritoneal dialysis are both effective at reducing serum phosphate concentration.

59.4.4.8 Hypophosphatemic Metabolic Alkalosis

Hypophosphatemia has an alkalinizing effect on the system but because phosphate levels are normally low, a decrease in phosphate will be life threatening before it creates a dramatic change in acid-base balance. Hypophosphatemia may be caused by malnutrition, nutritional disorders, excess renal excretion, or hemodilution. The result of decreases in phosphate is to increase the BE by 60% of the change from normal plasma concentration of inorganic phosphorus reported in mg/dl[6,9]:

$$\Delta \text{ BE } = 0.6 \times ([\text{ Normal phosphate }] - [\text{ Patient phosphate }])$$

Treatment is directed at careful intravenous phosphate replacement and treating the underlying cause.

59.4.4.9 Lactic Acidosis

Endogenous anaerobic metabolism produces lactic acid that dissociates to lactate plus a hydrogen ion. Hence hyperlactatemia is considered a cause of metabolic acidosis.[12] When the lactate anion is associated with a cation other than hydrogen ion, such as sodium as it is in lactated Ringer's solution, its acidifying effect is balanced by the alkalinizing effect of the strong cation it is paired with so that there is no net change in acid-base status.

Serum lactate (measured in mmol/L) will directly decrease the base deficit (more negative) as described by the following equation:

$$\Delta \text{ BE} = -1 \times ([\text{Patient lactate}])$$

If lactate is not measured directly, its effect on BE cannot be calculated and its impact will be accounted for within the unmeasured anion effect.

59.4.4.10 Increased Unmeasured Anions

Acid-base changes can be influenced by substances that are not measured in routine acid-base or chemistry panels. If the foregoing calculations successfully accounted for all the metabolic contributions to acid-base balance, the sum of the calculated effects of sodium, chloride, protein, phosphate, and lactate would equal the BE. In reality there is often a gap between their additive effects and the total BE. If a significant gap exists between the total BE and sum of the calculated effects it is indicative of the presence of unmeasured anions in the system.[6,9]

$$\text{UA}^{-} = \text{BE} - \text{Sum}$$

where Sum = sodium effect + chloride effect + protein effect + phosphate effect + lactate effect (if measured), and UA^{-} = unmeasured anions.

These unmeasured anions may include diabetic ketoacids, toxic acids (ethylene glycol, alcohols, salicylate), and the acids of renal failure other than phosphate.[1] If lactate is not measured and accounted for directly, hyperlactatemia will be reflected in the calculated unmeasured anion effect. When the clinician finds that a significant component of a decline in BE is due to unmeasured anions, a search for the more common causes should be initiated. Treatment for these disorders is directed at the underlying cause.

59.5 SUGGESTED FURTHER READING*

PD Constable: Clinical assessment of acid-base status: comparison of the Henderson-Hasselbalch and strong ion approaches. *Vet Clin Pathol*. **29**, 2000, 115, *A very detailed and precise discussion comparing the two most commonly used approaches to acid-base physiology. Possible difficulty working through some of the equations, but worth the effort.*

HAS de Morais, WW Muir: Strong ions and acid-base disorders. In JD Bonagura (Ed.): *Kirk's Current veterinary therapy XII: small Animal Practice*. ed 12, 1995, Saunders, Philadelphia, *An excellent treatise on strong ion concepts in acid-base disorders. May be the best introductory work for clinicians first attempting to learn strong ion concepts.*

SP DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders in small animal practice*. 2006, Saunders, St Louis, *The quintessential collection on veterinary fluid, electrolyte, and acid-base disorders. A good balance between basic information and supporting details that link the underlying research.*

V Fencl, A Jabor, A Kazda, J Figge: Diagnosis of metabolic acid-base disturbances in critically ill patients. *Am J Resp Crit Care Med*. **162**, 2000, 2246, *Much of the early work on adapting Stewart principles to the base excess algorithm method to determine the contribution of acid-base mediators done by Fencl*.

* See the CD-ROM for a complete list of references

60 Chapter 60 Lactic Acidosis

Jan P. Kovacic, DVM, DACVECC

60.1 KEY POINTS

- Lactate is synthesized from pyruvate and must be metabolized back to pyruvate to be removed. In anaerobic conditions, pyruvate cannot be used effectively in the Krebs cycle, so lactate levels rise.
- Lactic acid has an acidifying effect on plasma.
- Type A lactic acidosis is the hypoxic form. It occurs when there is inadequate oxygen delivery to the tissues.
- Type B lactic acidosis is the nonhypoxic form. It occurs when there are problems with cellular metabolism in aerobic conditions.
- Lactic acidosis occurs in health and disease. Elevations in lactate are common, but in health the lactate level is restored to normal very quickly after aerobic metabolism is restored.
- Normal lactate levels are less than 2 mmol/L.
- Persistently elevated lactate levels suggest a poor prognosis.

60.2 INTRODUCTION

Lactate is a 3-carbon molecule with a carboxyl group at one end that can accept a hydrogen ion to form lactic acid. The pKa for this hydrogen ion is 3.9. Like many of the organic acids of intermediate metabolism, lactic acid is dissociated completely at physiologic pH, and dissociation of the hydrogen ion leaves a strong anion. Consequently lactic acidosis can be recognized by changes in strong ion balance. According to the Stewart approach to acid-base analysis, strong anions force a change in aqueous solutions to increase hydrogen ion [H^+] and decrease hydroxyl ion [OH^-] concentrations and force a weak acid buffer such as carbonic acid to increase [H^+] and decrease bicarbonate concentration [HCO_3^-].[1-3] In the conventional approach to acid-base analysis, lactic acidosis is considered to be the consequence of the hydrogen ion production that occurs in conjunction with lactate metabolism. When the lactate anion is in association with another cation such as sodium, as it is in lactated Ringers solution, it does not have an acidifying effect.[1,3,4]

Lactate exists in two isomeric forms: d-lactate and l-lactate. d-Lactate is an important metabolic product of bacterial metabolism and has been reported to be clinically significant in man with short bowel syndrome, in cats fed propylene glycol, in cats with diabetes mellitus, and in a cat with exocrine pancreatic insufficiency.[1,4,5] l-Lactate is the isomer produced metabolically in dogs and cats and is the isomer discussed in this chapter. Most hospital analyzers measure only the L-lactate isoform, so d-lactate will be recognized as a metabolic acidosis with an increased anion gap or strong ion gap that is not accounted for by routine lactate measurement. Serum can be submitted to laboratories for specific d-lactate analysis.[4,5]

60.3 LACTATE METABOLISM

Lactate is synthesized from pyruvate and can also be converted back to pyruvate. This reversible reaction is catalyzed by the enzyme lactate dehydrogenase.[6] Lactate dehydrogenase has much greater binding affinity for l-lactate, so when d-lactate is present it is metabolized at a slower rate.

Lactate as an organic acid is unremarkable and behaves as do many other intermediary metabolites. What makes it remarkable is that it exists in a metabolic cul-de-sac with no way in or out except through pyruvate. During anaerobic metabolism when pyruvate is not efficiently metabolized via the Krebs cycle, lactate is formed in high concentration. This can occur with exercise or with disease. Lactate synthesis serves to regenerate nicotinamide adenine dinucleotide, an essential reducing equivalent for ongoing glycolysis. When aerobic conditions are restored, pyruvate is cleared, which opens the pathway for lactate to be metabolized back to normal levels. Lactate may also be transported in the blood and used in the liver under aerobic conditions for energy storage via gluconeogenesis and glycogen synthesis. This pathway involves reconversion of lactate to pyruvate in the liver (Cori cycle) under aerobic conditions to drive the Krebs cycle (Figure 60-1).[4,6]

Lactate is produced primarily in skeletal muscle, gut, brain, skin, and red blood cells. During anaerobic conditions, most lactate is produced in skeletal muscle and the gut. Lactate is metabolized primarily by the liver and kidney.

60.4 LACTIC ACIDOSIS

Lactic acidosis occurs whenever lactate production exceeds its utilization. This can occur with tissue hypoxia or in nonhypoxemic conditions when cellular metabolism is impaired.

Type A lactic acidosis is the hypoxic form. It can occur with true hypoxemia, severe anemia, reduced oxygen delivery from poor perfusion, or from dramatically increased tissue demand from exercise, convulsions, or heat stroke.[1,3,4,7]

Type B lactic acidosis is the nonhypoxic form. It occurs in the face of adequate oxygen delivery when mitochondrial oxidative function is abnormal. This can occur with drugs or toxins, hypoglycemia, diabetes mellitus, liver failure, renal failure, lymphosarcoma, sepsis, and inborn errors of metabolism (Box 60-1).[1,2,4]

60.5 CLINICAL APPLICATION

Lactate levels in plasma reflect the balance between continuous lactate synthesis, lactate breakdown, and the presence of an adequate circulating volume. For dogs the equilibrium state at rest produces a normal plasma lactate concentration of about 2 mmol/L, and for cats about 1.5 mmol/L.[1] Lactate concentrations above these levels should prompt immediate evaluation of the patient.

Lactate levels with exercise or with poor perfusion can increase over 10-fold without serious consequences as long as the increase is short-lived and adequate perfusion and aerobic conditions can be restored. Even with severe lactic acidosis (lactate >20 mmol/L), normal metabolic recovery when perfusion or oxygenation is restored can return the lactate to normal levels within 3 hours. The real problem occurs when increased lactate levels are sustained.

The most common forms of type A lactic acidosis are managed by adjusting the parameters of oxygen delivery:

$$\text{Oxygen delivery} = \text{Arterial oxygen content} \times \text{Cardiac output}$$

$$\text{Arterial oxygen content} = 1.34 \times \text{Hemoglobin (Hb) concentration} \times \%\ \text{Hb saturation} + 0.003 \times \text{Partial pressure of arterial oxygen}$$

$$\text{Cardiac output} = \text{Stroke volume} \times \text{Heart rate}$$

Management is therefore aimed at restoring an effective circulating volume and arterial oxygen content. With most acute-onset lactic acidosis, a rapid response to treatment is expected and lactate levels should decline with no long-term residual effects.

Sustained type A lactic acidosis is a consequence of either inadequate management or ongoing pathology such as aberrations of microcirculation or ischemic tissue. It is a very serious clinical finding that warrants immediate intervention. If cellular injury is extensive as a result of tissue hypoxia, type A lactic acidosis can convert to type B. In this instance oxygenation and circulation may be restored, but cellular injury is too extensive to reestablish normal metabolism and correct the lactic acidosis.

Sustained lactic acidosis can occur with type B, and improvement of perfusion and oxygenation will not resolve the problem. The clinician must identify the underlying cause of the disruption of cellular function and take steps to correct it. Toxins must be bound, metabolized, excreted, or dialyzed. Glucose metabolism must be normalized with adequate glucose supplementation, insulin therapy, or both. Septic patients probably have a combination of type A and type B lactic acidosis because, although oxygen levels may be adequate and perfusion is normal at the organ level, at the tissue level there is often enough disruption of microvascular perfusion such that many tissue beds are operating anaerobically. There may also be a hypermetabolic component that creates pyruvate faster than it can be metabolized in the Krebs cycle. In addition, sepsis can lead to acquired mitochondrial function defects and reduced lactate clearance.[1,2,4,7]

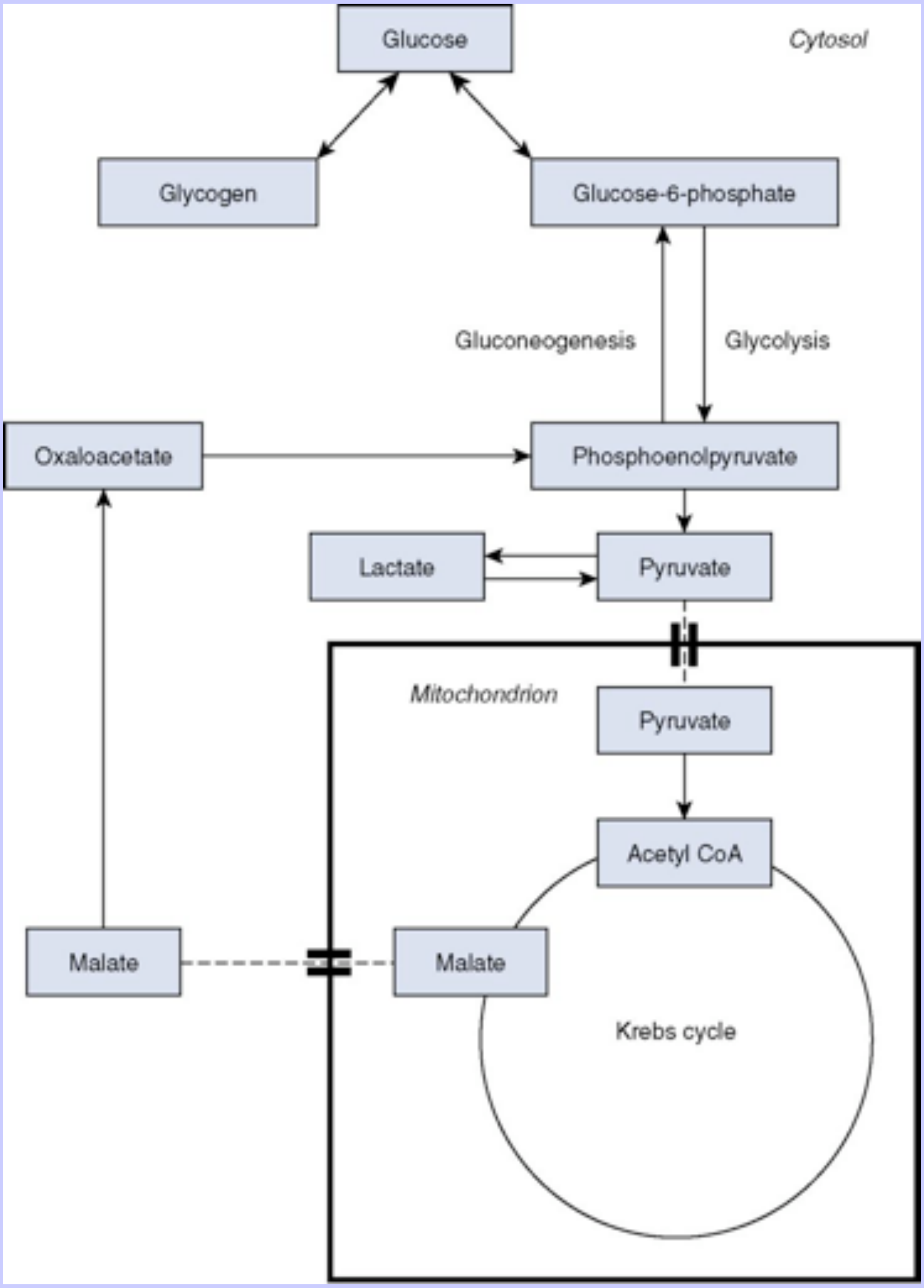
60.6 LACTIC ACIDOSIS WITH CARDIOPULMONARY ARREST

Cardiopulmonary arrest and cardiopulmonary resuscitation (CPR) create a special case of lactic acidosis. During the arrest state, perfusion and oxygen delivery fall to zero and tissue metabolism becomes anaerobic on a global scale. Plasma lactate levels measured in venous blood rise steadily. As CPR is initiated, lactate levels will continue to rise until effective tissue perfusion is achieved. The key to correcting the lactic acidosis of cardiac arrest is the return of spontaneous circulation.[1]

60.7 TREATMENT OF LACTIC ACIDOSIS

Treatment of type A (hypoxic) lactic acidosis is best accomplished by rapidly correcting the underlying cause. The use of sodium bicarbonate or other alkalinizing agents such as Carbicarb (an equimolar mixture of sodium bicarbonate and sodium carbonate), dichloroacetate, or THAM (tris-buffer) should be reserved for type B lactic acidosis that involves failure of cellular function that cannot be reversed, so primary treatment of the acidemia is the only therapeutic option.

Figure 60-1 Schematic of lactate metabolism in the cell. Under aerobic conditions with normal mitochondrial function, pyruvate enters the mitochondria and fuels the Krebs cycle. When pyruvate cannot enterthe mitochondrion it will be metabolized to lactate instead.



60.7.1

Box 60-1 Causes of Type B Lactic Acidosis

- Systemic inflammatory response syndrome
- Diabetes mellitus
- Malignancy—hematologic malignancies in particular
- Thiamine deficiency
- Liver failure
- Hypoglycemia
- Inborn errors of metabolism
- Mitochondrial myopathies
- Toxins
    - Cyanide
    - Ethanol
    - Ethylene glycol
- Drugs
    - Salicylate
    - Lactulose
    - β_2-Agonists
    - Nitroprusside
    - Acetaminophen
    - Propylene glycol
    - Phenformin

When treating type A lactic acidosis, while working to correct the underlying problem, the clinician may feel that the patient's pH is so low that the elevated hydrogen ion concentration has become the patient's most immediate problem. Severe acidosis does impair cardiovascular function and can be a serious barrier to resuscitating a patient in cardiopulmonary arrest. Alkalinizing agents such as sodium bicarbonate and Carbicarb may be used, but it is important to recognize that the lactic acidosis is not corrected with these agents. The acidemia improves, which may be helpful, but if spontaneous circulation is restored and the lactate is cleared quickly, the patient may be left with a hyperosmolar problem and an iatrogenic metabolic alkalosis. For this reason, sodium bicarbonate is rarely indicated for the treating of type A lactic acidosis. [2,4]

60.8 SUGGESTED FURTHER READING*

SP DiBartola (Ed.): *Fluid, electrolyte and acid-base disorders in small animal practice*. ed 3, 2006, Saunders, Philadelphia, *The quintessential collection on veterinary fluid, electrolyte, and acid-base disorders. A good balance between basic information and supporting details that link the underlying research.*

PJ Fall, HM Szerlip: Lactic acidosis: from sour milk to septic shock. *J Intensive Care Med*. **20**, 2005, 255, *An excellent review of lactate metabolism, types A and B lactic acidosis, and treatment of hyperlactatemia.*

D Hughes: Clinical use of lactate. In *Proceedings of the 11th International Emergency and Critical Care Symposium*. Veterinary Emergency and Critical Care Society, Atlanta, September 7-11 2005, *A fun and eclectic discussion of lactic acidosis with great clinical application. Includes many good references to human and veterinary studies that describe the clinical relevance of sustained elevations in plasma lactate.*

FC Luft: Lactic acidosis update for critical care clinicians. *J Am Soc Nephrol*. **12**, 2001, S15–S19, *A good review of lactic acid pathophysiology from the physician's perspective, with a discussion of therapies that directly address lowering the hydrogen ion concentration.*

RA Packer, LA Cohn, G Wohlstadler, et al.: d-Lactic acidosis secondary to exocrine pancreatic insufficiency in a cat. *J Vet Intern Med*. **19**, 2005, 106, *A very interesting case report of a cat with encephalopathy and gastrointestinal disease. Also provides a nice review of d-lactic acidosis.*

JG Salway: In *Metabolism at a glance*. ed 3, 2004, Blackwell, Oxford, *A wonderful book with large graphics that includes normal and abnormal pathways and a discussion of the pathophysiology behind the biochemistry. A great reference to have on hand when you need a reminder of what is happening at the biochemical level.*

SL Stockham, MA: Scott: In *Fundamentals of veterinary clinical pathology*. 2002, University of Iowa Press, Ames, IA, *A good veterinary clinical pathology reference. Includes an excellent basic review of both traditional Henderson-Hasselbalch acid-base physiology and also a discussion of strong ions.*

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* See the CD-ROM for a complete list of references

61 Chapter 61 Peripheral Venous Catheterization

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61.1 KEY POINTS

- There are four primary catheter types: winged, over-the-needle, through-the-needle, and multilumen.
- Catheter insertion site selection depends on several factors, including vessel availability and the intended purpose of catheterization.
- Proper vessel immobilization facilitates catheter placement.
- There are several catheter-related complications, phlebitis, thrombosis, catheter embolus, subcutaneous fluid infiltration, and infection, that can be minimized by appropriate attention to detail.

61.2 INTRODUCTION

Peripheral venous access is a cornerstone of the treatment of the emergency or critically ill patient. Patients often require temporary venous access for medications, fluid and electrolyte replacement, or transfusion of blood products. Medications and fluids with osmolalities 600 mOsm or less may be administered safely via a peripheral vein.[1] Site selection depends on the available vessels, condition of the vessels and patient, expense, and the urgency of the situation. Vascular access traditionally involves the insertion of a catheter into the cephalic, saphenous, or auricular vein; however, any visible vessel is a potential candidate for catheterization. Various techniques are used to insert catheters, including percutaneous, facilitative relief holes, and venous cutdowns.

61.3 CATHETER TYPES

A variety of catheters are commercially available (Figure 61-1). The length and gauge (diameter) of the catheter to be used are dependent on the species and size of the patient, the veins available and their condition, and the needs of the patient.

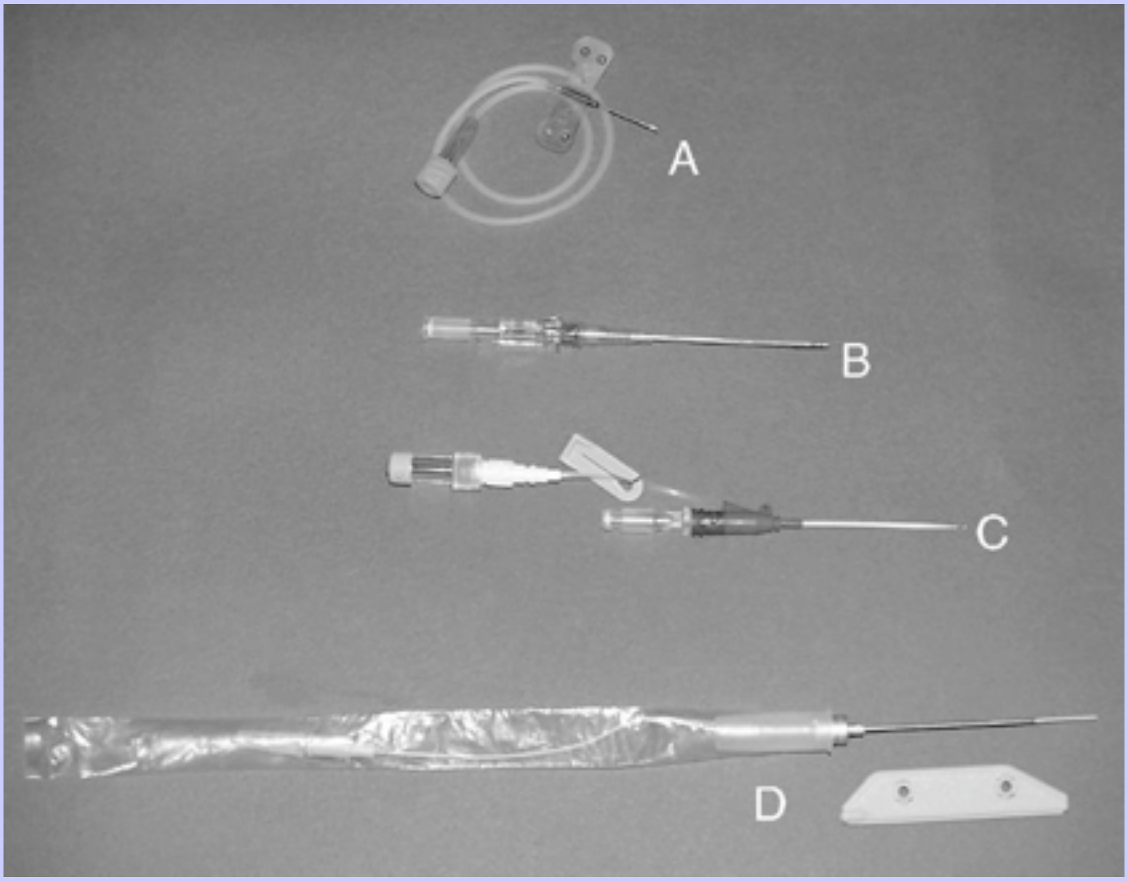
Both the radius and the length of the catheter determine the maximum flow rate. A large-gauge, short catheter is needed if fluids are to be administered rapidly, such as in a severely hypovolemic patient. If a slow infusion is acceptable, then a small-gauge catheter might be appropriate. A smaller catheter-to-vein ratio is considered more “vein friendly.”

There are four general categories of intravenous access devices. They include the winged needle, over-the-needle, through-the-needle, and multilumen catheters.

61.3.1 Winged or Butterfly Needle

The winged needle (butterfly) is for short-term use when the animal is not moving around very much. Applications might include blood collection or administration of nonirritating medications. Common needle size ranges from 25 to 19 gauge. The needles have plastic wings on the shaft to facilitate placement or taping in place. Plastic tubing of various lengths extends from the needle to the syringe connector port. These catheters are easy to place but difficult to maintain because of the ease with which the indwelling sharp needle punctures the vessel wall, allowing for subcutaneous infiltration of fluids or medications.

Figure 61-1 Example of various types of catheters: **A,** Winged needle or butterfly, **B,** over-the-needle catheter, **C,** TwinCath double-lumen catheter, and **D,** through-the-needle catheter with needle guard.



61.3.2 Over-the-Needle

The over-the-needle catheter is the most commonly used type. It is inexpensive and easy to place. The needle point extends a millimeter or so beyond the catheter tip. Over-the-needle catheters are available in a variety of lengths and gauges and are made of various materials (Teflon, polypropylene, polyvinyl chloride, and polyurethane).

61.3.3 Through-the-Needle

Catheters passed through the needle are called *through-the-needle* or *inside-the-needle catheters*. Through-the-needle catheters are usually longer (8 to 12 inches) than over-the-needle catheters and come in a variety of diameters. These catheters are used primarily in the jugular vein but can be used peripherally in the medial or 260 lateral saphenous veins. These catheters can be inserted to the level of the posterior vena cava, allowing for administration of hyperosmotic solutions. They can also be inserted into the cephalic vein but are often difficult to pass beyond the axilla into the larger anterior vena cava. A plastic sleeve prevents catheter contamination during insertion. Once the catheter is placed, the needle is withdrawn from the skin puncture site and covered with a needle guard to prevent the needle from shearing the catheter.

61.3.4 Multilumen

Arrow International (Reading, PA) produces a double-lumen over-the-needle catheter called a TwinCath. The TwinCath is more expensive than regular single-lumen catheters, but it allows simultaneous infusions of otherwise incompatible fluids via one catheter. Catheter placement is identical to that of any single-lumen over-the-needle catheter.

61.4 CATHETER INSERTION SITE

Peripheral insertion sites include the cephalic, lateral and medial saphenous, and the auricular vein.

61.4.1 Cephalic Vein

The cephalic vein is located on the anterior antebrachium. It crosses from the medial aspect of the leg an inch or so proximal to the carpus to join the brachial vein proximal to the elbow, which ultimately joins the external jugular vein. An accessory cephalic vein on the anterior aspect of the metacarpus passes over the carpus and joins the cephalic vein.[2] If possible, it is best to avoid the insertion of the catheter over the carpus, because it will be difficult to secure.

61.4.2 Saphenous Vein

The cranial branch of the lateral saphenous obliquely crosses the lateral aspect of the distal tibia.[2] The lateral saphenous vein is larger than the medial saphenous in the dog, and the medial saphenous is larger than the lateral and is more commonly catheterized in the cat.

61.4.3 Auricular Vein

The auricular veins are prominent in some breeds of dogs (Basset, Dachshund, and Bloodhound) and are fairly easy to catheterize.

61.4.4 Advantages of Peripheral Vein Catheterization

- Peripheral catheters tend to be relatively inexpensive, technically simple to place and well tolerated by most patients.
- Peripheral veins are easily accessible for quick catheterization such as in cardiac arrest or seizures. Two peripheral catheters may be indicated if rapid fluid resuscitation is required.
- Peripheral catheter placement generally requires minimal restraint. Patients suffering respiratory distress do not tolerate the stress of restraint (e.g., as would be required for central vein catheterization).

- Peripheral vein catheterization is generally associated with fewer significant complications such as hemorrhage, infection or thrombosis in comparison with central venous access.

61.5 INSERTION TECHNIQUE

61.5.1 Percutaneous

The area of the insertion site is generously shaved. Surgical preparation is performed with antiseptic scrub and solution. Aseptic technique is important to prevent indwelling catheter–related infection.[3] Proper aseptic technique may be bypassed in emergency situations, but these catheters should be removed once the crisis has passed.

Following skin preparation, the vein is occluded upstream of the insertion site by a tourniquet or an assistant. The distal portion of the leg is grasped in the palm of the hand of the operator and the leg is extended to tense and immobilize the vein. The thumb should not be used to stabilize the vein, because this compresses and collapses the vein. Flexion of the carpus will increase the stretch on the vessel and improve vessel immobilization in achondroplastic breeds. With the bevel up, the catheter is inserted through the skin at approximately a 15-degree angle. The catheter is advanced into the vessel; when blood appears in the flash chamber (hub), the needle and catheter are advanced as a unit for an additional 1 to 4 mm. This will ensure that the end of the catheter is entirely inside the lumen of the vessel. While holding the needle steady and maintaining the longitudinal tension on the leg, the catheter is then advanced off of the needle and into the vessel lumen. The catheter is capped with an injection cap or T-set and flushed with heparinized saline.

The technique for percutaneous catheterization of the auricular vein is similar to that for any peripheral vein. It may be useful to place roll gauze on the underside of the pinna to stabilize the ear.

Not all procedures are associated with spontaneous bleed back into the hub. If the operator thinks that the needle is in the vessel but does not see a flashback, the next step is to attach a syringe filled with heparinized saline and aspirate. Sometimes the flashback occurs, but following catheter insertion blood cannot be aspirated. There are two possibilities: (1) the catheter is in the vein but the vein collapsed around the end of the catheter, or (2) the catheter is not in the vein.

1. Excessive pressure to aspirate may collapse the vein; very gentle aspiration should be attempted.

   - The appearance of any amount of blood in the hub suggests proper placement; the operator should not expect free-flowing blood samples, because it is difficult to aspirate from many peripheral catheters.

   - The catheter tip may be occluded by a kink in the vein such as at the flexed elbow for a cephalic catheter; the leg should be extended.

   - The catheter may be large for the vein, obstructing blood flow past it; the vein should be occluded proximally and the foot squeezed to milk more blood into the vein.

   - If the catheter position still cannot be confirmed, inject a volume of saline into the catheter while watching for a subcutaneous bleb. If a large volume of saline can be injected without forming a subcutaneous bleb, the catheter must be in the vein.

2 The catheter may not be in the vein even though a flashback of blood was observed initially, and this can be attributed to several common technical missteps.

- After the flashback, the tension on the leg and skin was relaxed, allowing the vein to retract off the end of the needle; the tension must be maintained until after the catheter is inserted.

- The flashback was associated with the needle tip being in the vein, but the catheter tip was not wholly within the lumen of the vein; when the catheter was introduced it pushed the vein off the needle.
- The needle-and-catheter unit must be inserted a short distance beyond initial vein entry. Sometimes when the needle-and-catheter unit is advanced, it passes through the deep wall of the vein; the catheter will be pushed through the vein. If this is suspected, the needle-and-catheter unit is carefully withdrawn until backflow is evident ("catch the lumen on the way out"). Then readvancing the catheter into the vessel in the routine manner can be tried.

61.5.2 Facilitative Incision or Relief Hole

Failed catheterization attempts may also be caused by catheter flaring. Flaring of the tip of the catheter may occur when the tip is torn or peeled back during its insertion through the skin. After a failed attempt, inspect the catheter tip for such flaring before reuse. A facilitative incision or relief hole reduces the skin tension and friction against the catheter, minimizing catheter flaring, and is an especially important procedure in severely dehydrated patients or those with tough skin. A facilitative incision may be made with a No. 11 scalpel blade or a 20-gauge needle. A 0.5-mm incision is made directly over the vessel, extending through the dermis and taking care to avoid lacerating the underlying vessel. Local anesthetic blocks are rarely needed; intradermal or subcutaneous lidocaine stings. Following the facilitative procedure, the catheter is inserted as previously discussed.

61.5.3 Venous Cutdown

A venous cutdown is indicated when the veins are small (small patients, or patient that is severely hypovolemic) or when the veins are obscured (obesity, subcutaneous edema, or hematoma). Following aseptic skin preparation awake animals will require local anesthesia of the region, taking care not to inject any agent intravenously. A 1- to 2-cm incision is then made through the skin parallel to the vessel, being careful not to lacerate the vein. The vessel is dissected free of the surrounding tissue. An encircling suture is placed around the vein proximal and distal to the intended venotomy site. The catheter can be inserted directly through the superficial vessel wall or, if a catheter is to be used without a needle, an incision can be made into the vein while applying traction on the preplaced sutures. If an incision is made, once the catheter is inserted, both sutures are tied proximally to prevent bleeding (Color Plate 61-1). The skin is closed and the catheter site is bandaged.

61.5.4 Peripherally Inserted Central Venous Catheters

Central venous catheterization can be achieved by passing a long catheter from a peripheral insertion site to a central vessel. This can allow easy sample aspiration, administration of hypertonic fluids, and long-term catheter maintenance (see Chapter 63, Central Venous Catheterization).

61.6 COMPLICATIONS ASSOCIATED WITH CATHETERIZATION

61.6.1 Phlebitis

Phlebitis is inflammation of the vessel wall occurring as a result of damage to the endothelial lining. Phlebitis is characterized by swelling, tenderness on palpation, and erythema of the skin over the vessel. Phlebitis may be caused by the following:

1. Mechanical damage to the vessel by movement of the catheter, so it should be well stabilized.
2. Administration of hyperosmotic fluids; the osmolality of peripherally administered fluids should not exceed 600 mOsm.
3. Infection; aseptic technique should be maintained at all times if possible.

Some patients seem prone to catheter phlebitis for no apparent reason despite good technique.

61.6.2 Thrombosis

Thrombosis is the formation of a thrombus on the catheter or vessel wall (as a consequence of phlebitis). Thrombosis can result from endothelial trauma or an inflammatory reaction to the catheter material. A vein that "stands up" without being held off and feels thick and cordlike characterizes thrombosis.

61.6.3 Catheter Embolism

Catheter embolism occurs when a fragment of the catheter breaks off and enters the circulation. The fragment may be severed when withdrawing an inside-the-needle catheter. It can also occur if the catheter is cut during bandage change or the patient molests its bandage.

61.6.4 Subcutaneous Fluid Infiltration

Infiltration of fluids into the tissues surrounding the vein may occur if:

1. The catheter was never in the vein in the first place.
2. The catheter is displaced out of the vein by excessive skin movement.
3. Upstream vein occlusion by thrombosis has occurred.

Signs of infiltration are swelling and tenderness around the insertion site.

61.6.5 Infection

An indwelling catheter is an excellent pathway for microorganisms to enter the tissues and the venous system. Infection may be heralded by phlebitis and cellulitis (a purulent discharge from the insertion site). Aseptic technique in catheter placement and maintenance will help to decrease the risk of infection. Fever of unknown origin in a critically ill patient should prompt consideration of replacement of all indwelling catheters.

61.7 CATHETER MAINTENANCE

Intravenous catheter care should be performed every 48 hours or on an as-needed basis if the site gets soiled. The catheter dressing should be removed and the site inspected. Look for clinical signs of phlebitis, infection, and thrombosis and, if present, the catheter should be removed. While flushing the catheter with heparinized saline, the insertion site should be observed for fluid leakage or pain during injection. If either is observed, the catheter should be removed.

If any portion of the catheter is exposed, this should be recorded in the medical record and the catheter should not be reinserted. If the catheter site looks good, the site should be cleaned with an iodophor or chlorhexidine solution. When the catheter site is dry, a sterile 2 × 2 gauze pad is placed over it and the bandage reapplied.

Traditionally it has been recommended not to leave a catheter in place any longer than 72 hours. These recommendations come from human medicine. The likelihood of complications increases the longer a catheter is left in place.[3] It has been our experience that as long as routine catheter care is performed, and the catheter removed when problems are first noticed, one can often exceed the 72-hour rule. A study looking at peripheral and jugular venous catheter contamination in dogs and cats supports our experience.[4]

Intravenous catheters should be observed several times a day. If the catheter bandage is wet, the reason should be identified and the bandage should be changed. Swelling distal to the catheter may be indicative of an excessively tight bandage or tape. Swelling proximal to the catheter may be due to infiltration.

61.8 Suggested Further Reading*

C Burrows: Inadequate skin preparation as a cause of intravenous catheter-related infection in the dog. *J Am Vet Med Assoc*. **180**, 1982, 747, *A very interesting prospective study in which significantly more venous catheters placed without aseptic skin preparation (48%) had a positive bacterial culture at the time of removal compared with those placed using aseptic technique (15%) in a total of 88 dogs*.

HE Evans: In *Miller's anatomy of the dog*. 1993, Saunders, Philadelphia, *The bible of veterinary anatomy*.

B Hansen: Technical aspects of fluid therapy. In SP DiBartola (Ed.): *Fluid, electrolyte and acid-base disorders in small animal practice*. 2006, Saunders, St Louis, *Fluid therapy chapter that includes a discussion of catheter selection and placement techniques; includes an excellent discussion of skin preparation for venous catheterization*.

KA Mathews, MJ Brooks, AE Valliant: A prospective study of intravenous catheter contamination. *J Vet Emerg Crit Care*. **6**, 1996, 33, *A prospective study that found no association between dwell time and incidence of intravenous catheter contamination in a veterinary intensive care unit.*

* See the CD-ROM for a complete list of references

62 Chapter 62 Intraosseous Catheterization

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62.1 KEY POINTS

- Intraosseous catheterization is an emergency procedure that allows access to the central circulation comparable to that achieved with a central venous line.
- Intraosseous catheterization is indicated when emergency vascular access is required and intravenous access can not be performed in a timely manner.
- Intraosseous catheterization is an easy, fast, and inexpensive technique that can be performed effectively in various species.
- Intraosseous infusion is contraindicated in recently fractured bones, those in which catheterization has been already attempted, and pneumatic bones of birds.
- The rate of complications for intraosseous infusion is extremely low, and osteomyelitis is the major risk.
- Blood samples obtained from intraosseous catheters can be analyzed for some hematologic, biochemical, and blood gas parameters in steady-state, low-flow conditions, and during the early phase of cardiopulmonary resuscitation.

62.2 INTRODUCTION

Rapid establishment of vascular access is crucial in critically ill patients, particularly those with life-threatening conditions. In animals with hemodynamic failure, peripheral vessels may constrict or collapse and grossly disappear. Finding and cannulating vessels is particularly challenging in small and neonatal patients. Attempts to catheterize a peripheral vein can be frustrating, time consuming, and unsuccessful even for the most skilled personnel. In pediatric prehospital and emergency department settings, peripheral intravenous access could not be obtained in 6% of patients and required over 10 minutes in 24%, with significantly prolonged times in children under 2 years of age.[1]

Compared with percutaneous peripheral vein catheterization, both surgical cutdown and central venous line placement increase the likelihood of successful circulatory access, but they require greater expertise and more time.[1,2] Peripheral venous catheterization within 90 seconds is successful in only 18% of cases. The success rate increases to 37% with subsequent percutaneous femoral vein catheterization.[2]

There are limited alternative routes for drug delivery in cases that require cardiovascular support but lack venous access. The endotracheal route is a last-resort option recommended by the American Heart Association for some resuscitation drugs during cardiac arrest in both adult and pediatric patients.[3,4] This route obviously can not provide for fluid resuscitation, and even for commonly recommended drugs such as epinephrine the clinical effect is less predictable than when intravenous administration is used.[5] Additionally, the dosage of intratracheal epinephrine has to be increased up to 10-fold.[6] Furthermore, lower circulating epinephrine concentration, from endotracheal administration, could result in counterproductive β_2-adrenergic stimulation, which leads to peripheral vasodilation, low diastolic aortic pressure, and decreased myocardial perfusion pressure.[6]

Two proposed but inadvisable routes of drug administration are the sublingual and intracardiac routes.[7] Intracardiac injections are associated with risks (e.g., hemopericardium, coronary artery perforation, myocardial ischemia, arrhythmias) that exceed the benefits. Alternatives to intravenous access are reported,[7] but they are indicated mainly for volume replacement in states of dehydration (subcutaneous or intraperitoneal infusion) and are not effective for hypovolemia.

Curiously, an unusual emergency vascular access, such as corpus cavernosum, was demonstrated to be fast and feasible for fluid resuscitation in dogs with severe hypovolemia, offering new therapeutic perspectives, even if limited to male dogs.[8] In pediatric and adult patients, intraosseous access is now recommended as the first choice if intravenous access is unavailable.[3,4] The intraosseous route is safe, practical, and reliable for fluid resuscitation, drug administration, and even blood sampling for analysis. This chapter focuses on what makes the intraosseous route suitable for fluid infusion and drug administration. The main indications, contraindications, complications, procedures, and future perspectives for intraosseous access in veterinary patients will be presented based on veterinary reports, human studies, and experimental animal models.

62.3

HISTORICAL PERSPECTIVES

The possibility of perfusing the tibia of the dog was demonstrated in 1922 by Drinker and colleagues, who were studying vascular physiology of the bone marrow.[9] Starting from this scientific observation, the potential use of the intraosseous route for parenteral infusion of drugs and fluids was addressed by several studies in Europe and North America during the 1930s and 1940s.[10-12] In rabbits, intraosseous infusions of whole blood and hypertonic glucose solutions rapidly corrected anemia and hypoglycemia, respectively.[10] In dogs, intramedullary injection of citrated blood into the sternum effectively restored blood volume.[11] Moreover, an injection of epinephrine into the marrow of the tibia resulted in a clinical response similar to that achieved by injection into the femoral vein.[11]

Intraosseous infusion was established as a reliable and safe technique for rapid, short-term access into the central circulation in adults and children when veins were inaccessible (e.g., peripheral circulatory failure, burns, and very young patients).[11,12] However, with the introduction of plastic catheters for peripheral venous access during the late 1950s, intraosseous infusions fell into disuse.[1,13] A renewed interest in the intraosseous procedure appeared during the 1980s because of its utility in hypotensive patients and efficacy for the administration of lifesaving drugs.[14] The intraosseous route was recommended as an alternative emergency access in pediatric advanced life support for children under 6 years of age and, more recently, resuscitation guidelines extended its use to children of any age and even to adults.[3,4]

62.4

PHYSIOLOGY

The bone marrow is a semifluid blood-forming tissue enclosed in a nonexpandable bony case. This protective osseous coating prevents bone marrow vessels from collapsing during peripheral circulatory failure. A rich capillary network drives substances injected into the marrow to the large medullary venous channels and quickly through the nutrient and emissary veins to the central circulation.[9-11]

Several types of fluids (blood and blood components, colloids, crystalloids)[11] and several drugs,[15] administered through an intraosseous, a central, or a peripheral intravenous line, are equally effective in reaching the central circulation despite normotensive, hypotensive, or arrest conditions.[14-16] Particularly during hemodynamic failure, intraosseous infusion of resuscitative fluids (e.g., hydroxyethyl starch) and drugs (e.g., sodium bicarbonate) seems to guarantee a higher magnitude of the peak effect and even a prolonged duration of action compared with peripheral venous administration.

Although intraosseously administered drugs reach peak effect more slowly[14,15] because of a reduction in blood flow and an increase in vascular resistance in the bone marrow during systemic hypotension, this effect can be overcome partially by pressurized infusion, especially when using viscous fluids likes colloids, or by a fluid bolus following the injection of a drug into the intraosseous space.[15] Mean intraosseous infusion flow rates of crystalloid solutions delivered under pressure (300 mm Hg) are limited to approximately 29 ml/min in puppies[17] and 47 ml/min in foals. Thus rapid delivery (90 ml/kg within 30 minutes) of fluids during severe hypovolemia may not be possible in dogs that weigh more than 10 kg. However, intraosseous infusion of hyperoncotic, hypertonic, and even crystalloid solutions effectively reversed hypotension in several animal models of hemorrhagic shock (see Chapter 65, Shock Fluids and Fluid Challenge).[18,19,22,23]

62.5 INDICATIONS

There are no studies documenting the incidence or impact of intraosseous catheterization in veterinary medicine. Most of the indications have been extrapolated from human experience and experimental animal models.[7,12,17] The information obtained from pediatric patients, in whom the time required to complete an intraosseous catheterization can be less than 1 minute with over 70% to 80% success, may be particularly relevant to small and neonatal animals.[18,19]

Early implementation of the intraosseous route as an alternative to failed intravenous access is now widely accepted and is included in the guidelines for management of cardiac arrest in pediatric and adult human patients. These recommendations are applicable to veterinary patients as well, particularly for small and neonatal animals whose veins can be difficult to visualize normally and tend to grossly disappear completely during shock. Fluid resuscitation through an intraosseous catheter can restore a vascular volume sufficiently to allow subsequent catheterization of a peripheral vein.

Conditions such as peripheral vascular thrombosis, peripheral edema, status epilepticus, obesity, and burns may be indications for obtaining intraosseous access.[13,18,19] An additional advantage of intraosseous catheterization during 264 emergency situations is the potential for blood sampling. Initial assessment of hematologic, biochemical, and acid- 265 base status and subsequent monitoring of the therapeutic response are essential in critically ill patients. Blood sampling, however, can be challenging during cardiovascular collapse.

The reliability of results obtained from blood collected from intraosseous lines has been investigated in both steady-state and circulatory failure conditions. In normal animals, hemoglobin, hematocrit, some biochemical param-eters (blood urea nitrogen, creatinine, total solids, albumin, bilirubin, sodium, chloride, calcium, phosphorus) and blood gases are sufficiently comparable to those of peripheral or central venous blood to be of clinical value. Values obtained for potassium and glucose, however, need to be interpreted with caution.[20,21] Acid-base values from intraosseous samples in cardiopulmonary resuscitation (CPR) models reflect the mixed venous blood acid-base balance during the first 15 minutes of CPR, and beyond that time values can be influenced by local acidosis.[22,23] In one CPR study, intraosseous and central venous blood biochemical and hemoglobin values remained similar for the first 30 minutes if the intraosseous site was not used for drug infusions.[24]

62.6 CONTRAINDICATIONS

The only absolute contraindication to intraosseous catheterization is a fracture in the bone to be used. In cases of failed intraosseous catheter placement where the cortex has been penetrated, the risk of fluid or drug extravasation increased.[13,19] To minimize risk, a second cannula of larger diameter should be placed through the same entry site or preferably a separate bone should be used. Intraosseous infusions in pneumatic bones of birds are contraindicated. Clearly, intraosseous catheters should not be placed through infected tissues. Sepsis and septic shock have been suggested as contraindications for intraosseous lines; however, reported complication rates in septic children were low.[1]

62.7 METHODS

The increased use of intraosseous catheterization during the last 15 to 20 years[1,19] has been accompanied by the development of new medical equipment. Intraosseous catheters range from traditional manually placed hypodermic needles to the newly dedicated catheters with automated delivery systems.[19,24] The main requirements of any intraosseous delivery system are ease of handling, ability to reload, small expense, and adaptability to most conditions. The supplies necessary for an intraosseous catheterization kit are described in Box 62-1.

Commercial disposable intraosseous infusion needles with a central stylet (Cook Critical Care; Bloomington, IN; Cardinal Health, McGaw Park, IL.) are designed to penetrate the bony cortex, prevent occlusion of the cannula lumen, and establish rapid access to the marrow sinusoids and vascular system.[19] However, an 18- to 30-gauge hypodermic needle is useful in neonates with soft cortical bone, an 18- to 22-gauge spinal needle is excellent in cats, small dogs, and birds, and a bone marrow or intraosseous infusion needle is essential in mature dogs.[18]

A bone injection gun is a spring-loaded, impact-driven intraosseous device developed for use in pediatric and adult humans. It propels the intraosseous cannula at high speed through skin, subcutaneous tissues, and bone cortex to a fixed depth. This automatic device was significantly faster than a standard Jamshidi bone marrow needle in obtaining intraosseous access in the proximal tibia of dogs.[24] The high speed of insertion helps to minimize pain; however, local anesthesia is recommended in conscious patients.[24]

62.7.1 Box 62-1 Supplies Necessary for an Intraosseous Catheter Kit

- Topical antiseptic
- Sterile gloves
- Local anesthetic for the skin and periosteum
- A scalpel blade for making a stab incision through the skin
- Needles
    - Hypodermic (18- to 30-gauge)

  - Spinal (18- to 22-gauge)
  - Bone marrow or intraosseous infusion needles (Figure 62-1, Jamshidi/Illinois, Cardinal Health, or Cook Critical Care)
- Bone injection gun: Optional device for more rapid access to the intraosseous space (Figure 62-2, WaisMed Ltd Houston, TX)
- Syringe for aspiration of bone marrow to confirm correct placement and potentially collect samples for hematologic or biochemical analysis
- Heparinized saline solution
- Fluid with administration set or catheter cap and a pressure bag
- Mechanism to secure the catheter:
  - Tape butterfly and suture material
  - Cyanoacrylates to secure suture directly to hub of needle
  - Commercial intraosseous catheter with flange
  - Bandaging material
- Triple antibiotic ointment or appropriate antiseptic ointment or cream

Figure 62-1 Intraosseous infusion needle. Courtesy Cardinal Health.

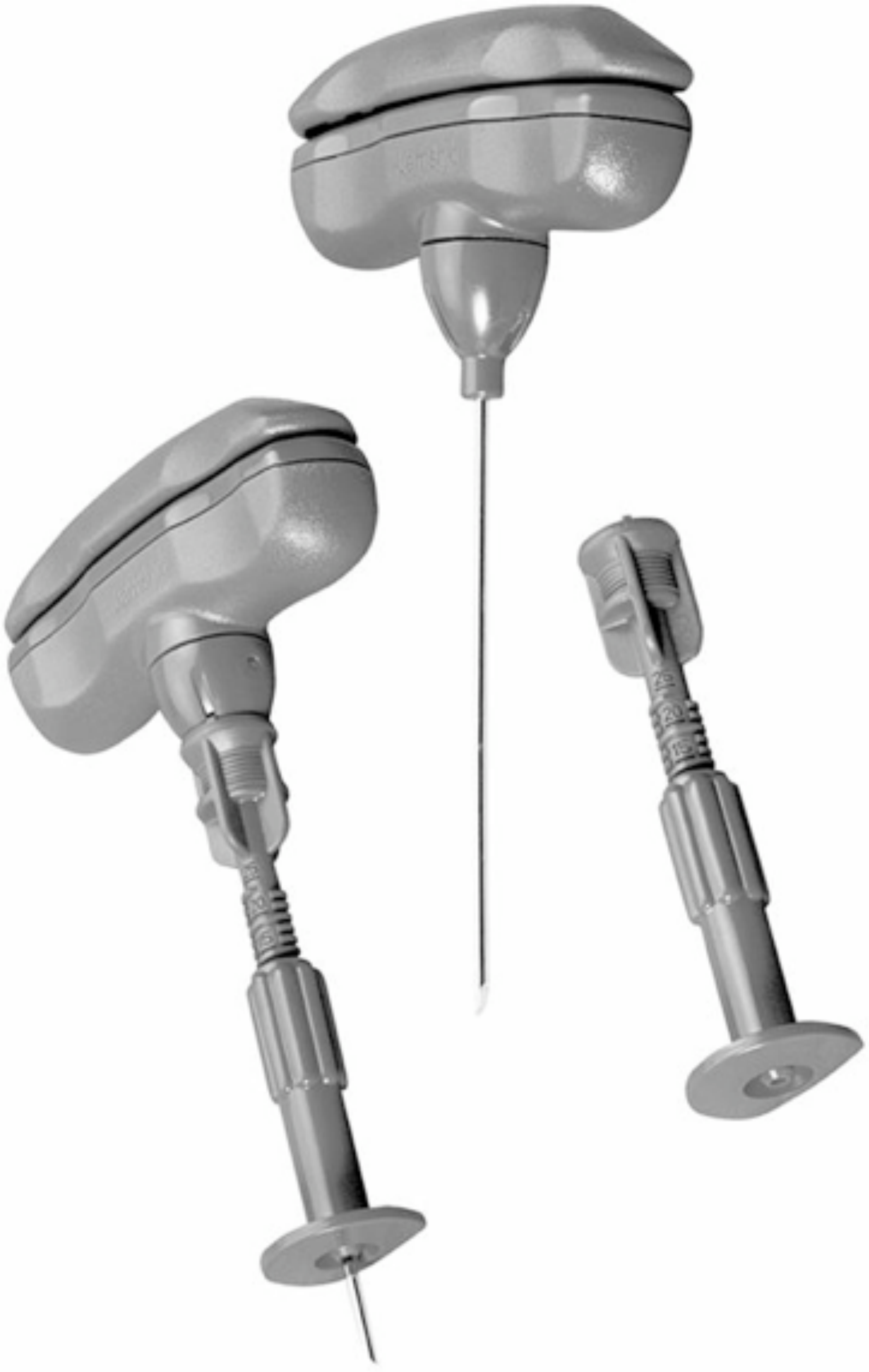
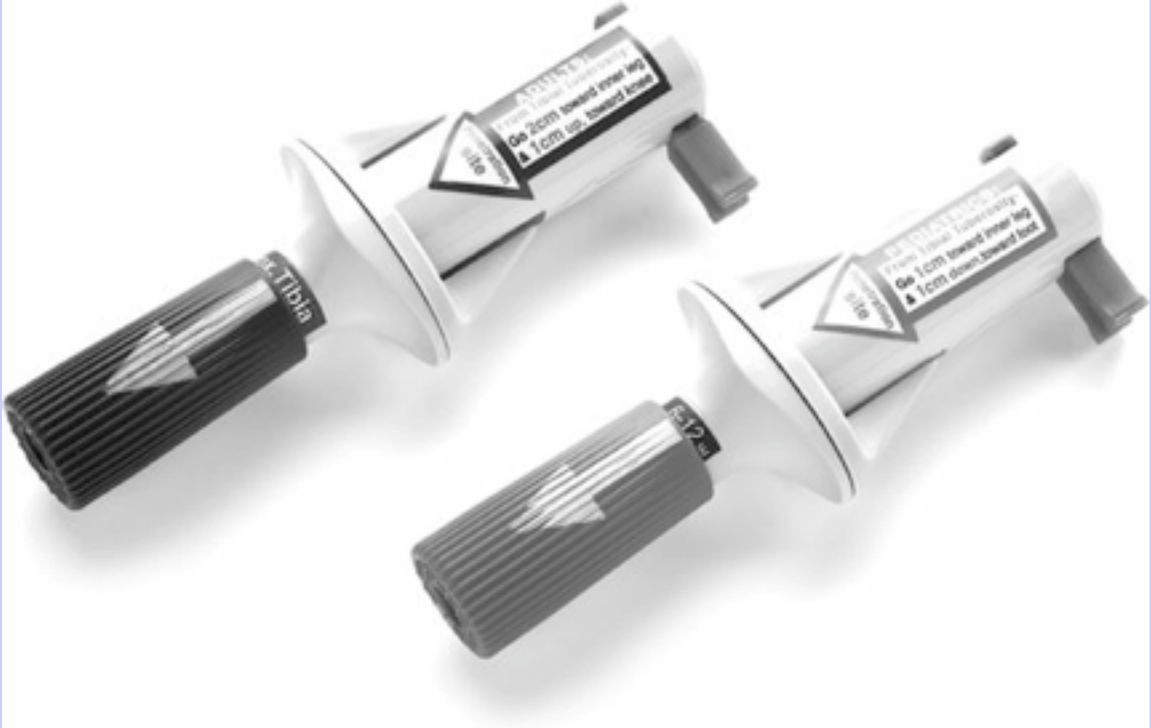


Figure 62-2 Bone injection gun. Courtesy WaisMed Ltd, Houston, TX.



Other devices such as a drill for intraosseous access (EZ-IO, Vida Care, San Antonio, TX) and a sternal intraosseous device (FAST1, Pyng Medical, Richmond, BC, Canada) are now available.[19] Applications in veterinary medicine still need to be verified.

The access site should be easily accessible and should not interfere with ongoing procedures such as CPR. The most commonly used sites include the flat medial surface of the proximal tibia (1 to 2 cm distal to the tibial tuberosity), the tibial tuberosity itself, or the trochanteric fossa of the femur (Color Plate 62-1). Alternative approachable points can be considered such as the wing of the ilium, the ischium, and the greater tubercle of the humerus.[18,25] However, no studies in animal patients suggest any one site to be superior. Finally, the choice of a particular site will depend on the experience and preference of the clinician, the anticipated duration, and the mobility of the patient. The trochanteric fossa of the femur seems to be well tolerated, allows mobility, and is generally easy to place.[18] In obese or very edematous animals or those in status epilepticus, the tibia is probably more accessible.[18]

In humans, alternative sites include sternum, radius, ulna, and calcaneus.[19] Aseptic preparation of the site is required. The periosteum is highly innervated; therefore in stable patients, local infiltration with local anesthetic (e.g., 1% lidocaine) is recommended. A preemptive skin stab incision over the site of penetration of the catheter may prolong the life of the needle.

For placement in the medial tibia, the needle must be directed into the bone slightly distally and away from the proximal growth plate. To prevent sciatic nerve involvement during placement in the femur, the needle should be walked off the medial aspect of the greater trochanter into trochanteric fossa, with the hip joint in a neutral and internally rotated position. Once the desired orientation of the needle is reached, firm pressure should be applied in clockwise, then counterclockwise rotation. This procedure normally generates a small depression that seats the needle in the bone; by increasing the pressure maintaining the same rotation pattern, the needle should proceed through the near cortex. A sudden loss of resistance indicates that the needle has crossed the cortex.

Before administration of fluids or drugs through an intraosseous catheter, verification of correct placement is required. One of the most frequently reported causes of failure of intraosseous catheterization is an error in identifying landmarks. A well-positioned catheter should be firmly seated in the bone and move with the limb without being dislodged. Gentle aspiration should bring bone marrow into the syringe, although in older animals this may not always be possible. A bolus of heparinized saline solution should flow easily, and there should be no accumulation of fluid in the subcutaneous tissue.

If resistance is encountered, the needle can be rotated 90 to 180 degrees to move the beveled edge away from the inner cortex. The subcutaneous tissue must be observed for fluid extravasation. If extravasation is detected, the needle should be removed to prevent further complications and an alternative bone should be chosen for catheter placement. Once correct placement of the needle is verified, administration of fluids or drugs can be started by syringe or by using a standard intravenous administration set. To maintain patency during intermittent usage, a catheter plug can be applied and the catheter flushed with heparinized saline solution.

Initial infusion of fluids under pressure causes pain, lasting approximately 1 to 2 minutes, in conscious human patients. In humans, recommendations to minimize pain include withdrawal of a small volume of bone marrow, and slow injection of 1% lidocaine over 60 seconds before initiating the infusion. To properly secure the needle, a tape butterfly can be wrapped around the hub and sutured to the skin or the periosteum. The suture may also be fixed to the hub of the needle with a cyanoacrylate glue. Some intraosseous needles come with permanent butterflies for suturing.

Coverage of the area with antiseptic or antibiotic cream is suggested and, when possible, a protective bandage can prevent damage to the needle. Intraosseous catheters require the same nursing care as intravenous catheters. In most cases, the intraosseous catheter is considered a temporary access that should be replaced by an intravenous catheter as soon as possible. When prolonged intraosseous infusion is required, guidelines for intravenous catheter care should be followed. Although there are limited data, the risk of complications is thought to be minimal for catheters remaining for up to 72 hours with proper maintenance.[18,25]

62.8 COMPLICATIONS

The documented complication rate associated with intraosseous infusions in humans and animals is low. The types of complications include infection, fat embolism, extravasation of fluids, compartment syndrome, and bone fractures.[13,19] One of the most common concerns when performing intraosseous infusion is osteomyelitis. Proper sterile technique during placement reduces the risk of infection to 0.6% of cases, with potentially lower risk if the catheter is removed as soon as intravenous access is established or within 72 hours.[1]

Several studies have demonstrated that administration of fluids and drugs through an intraosseous route does not impair bone growth.[26] Fat embolism can occur during intraosseous infusion; however, evidence for clinical significance is lacking. Although unlikely with proper technique, extravasation of fluids and compartment syndrome can be associated with major morbidity in humans. Improper catheter placement combined with irritating or hypertonic fluids, high fluid rates, pressure infusion, and large infusion volumes can all predispose to extravasation of fluids and compartment syndrome.[13,19] The latter does not appear to be a major issue in animals; however, if any infiltration is detected the intraosseous infusion should be discontinued immediately. In addition, it is imperative that no additional catheter be placed in the same bone.

Intraosseous infusion of hypertonic solutions is effective and apparently safe from major and long-term complications. Soft tissue and bone marrow necrosis secondary to intraosseous infusion of hypertonic saline has been reported in piglets, in which major clinical signs developed 48 hours postoperatively; therefore caution should be exercised when using hypertonic solutions.[27] Finally, appropriate insertion technique, asepsis, frequent monitoring of the intraosseous access site, and prompt removal of the needle once an intravenous line has been established help to reduce risk factors and complication rates.

62.9 SUGGESTED FURTHER READING*

S DeBoer, M Seaver, C Morissette: Intraosseous infusion: not just for kids anymore. *Emerg Med Serv*. **34**, 2005, 54, *A practical and updated nursing review describing the main indications for intraosseous infusion in humans and looking at the available devices*.

CM Otto, MG Kaufman, DT Crowe: Intraosseous infusion of fluids and therapeutics. *Comp Cont Educ Pract Vet*. **11**, 1989, 42, *One of the early review articles that resurrected the use of intraosseous infusions in veterinary practice, including a series of cases and technique*.

LM Tocantins: Rapid absorption of substances injected into the bone marrow. *Proc Soc Exp Biol Med*. **45**, 1940, 292, *One of the first and most cited studies of intraosseous infusion in animals*.

* See the CD-ROM for a complete list of references

63 Chapter 63 Central Venous Catheterization

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63.1 KEY POINTS

- Indications for central venous catheter placement include hemodynamic monitoring, drug administration, and serial blood sampling.
- Saphenous veins can be used as access points to the central venous circulation.
- Medications with osmolalities of greater than 600 mosm/L should be administered via a central vein.
- Multilumen catheters minimize the number of veins that need to be catheterized.
- Patient positioning and immobilization of the vein are key to successful catheterization.

63.2 INTRODUCTION

Central venous catheters terminate in the cranial or caudal vena cava. These catheters may be inserted directly into a large central vein such as the jugular vein or inserted via a peripheral vein: a peripherally inserted central catheter (PICC). Indications for central venous catheter placement include hemodynamic monitoring, drug administration, and serial blood sampling.[1] Central venous catheters often can be left in place for longer periods than peripheral catheters, making them very useful in critically ill patients. The following are situations in which a central catheter may be preferable to a peripheral venous catheter:

- Administration of multiple fluid and drug types that are not compatible with each other, necessitating multiple catheter lumens
- Administration of fluids that have an osmolality greater than 600 mosm/L and constant rate infusions of drugs known to cause phlebitis, such as diazepam, pentobarbital, and mannitol
- Measurement of central venous pressure
- Frequent aspiration of blood samples
- Total parenteral nutrition administration
- Maintenance of venous access for long periods
- When peripheral catheters are at risk of contamination from vomiting, polyuria, diarrhea, or vaginal discharge, because it may be easier to keep a jugular catheter site clean
- To facilitate transvenous pacing

63.3 GENERAL CONCEPTS

Because introduction of foreign material or infectious agents into the central circulation can have far more serious consequences than peripheral vessel contamination, maintenance of aseptic technique when placing and using central venous catheters is of utmost importance (see Chapter 116, Catheter-Related Bloodstream Infection). General recommendations for central venous catheter maintenance is to wipe all injection ports with alcohol before needle puncture, keep insertion sites bandaged, prevent catheter hubs dragging on the ground, and immediately respond to witnessed catheter contamination. This may require cleaning and changing injection ports and fluid lines, or it may necessitate catheter removal. Inadvertent disconnection of fluid lines from a central venous catheter or animal-induced trauma to the catheter can lead to significant hemorrhage. Leaving ports of a central venous catheter open to the atmosphere places the patient at risk of air embolism. For this reason the catheter should be occluded by a catheter lock or manual kinking whenever the catheter hub is open to the atmosphere (e.g., when connecting and disconnecting syringes for blood aspiration).

63.4 CATHETER TYPES

Through-the-needle, long over-the-needle, long single-lumen, multilumen catheters, and catheter introducers can all be used to access central veins (Figure 63-1).[1-3]

63.4.1 Through-the-Needle

Through-the-needle catheters were discussed in Chapter 61, Peripheral Venous Catheterization. They commonly are used to catheterize jugular veins. The Drum-Cartridge is a very long through-the-needle catheter that is an effective PICC for large patients (see Figure 63-1).

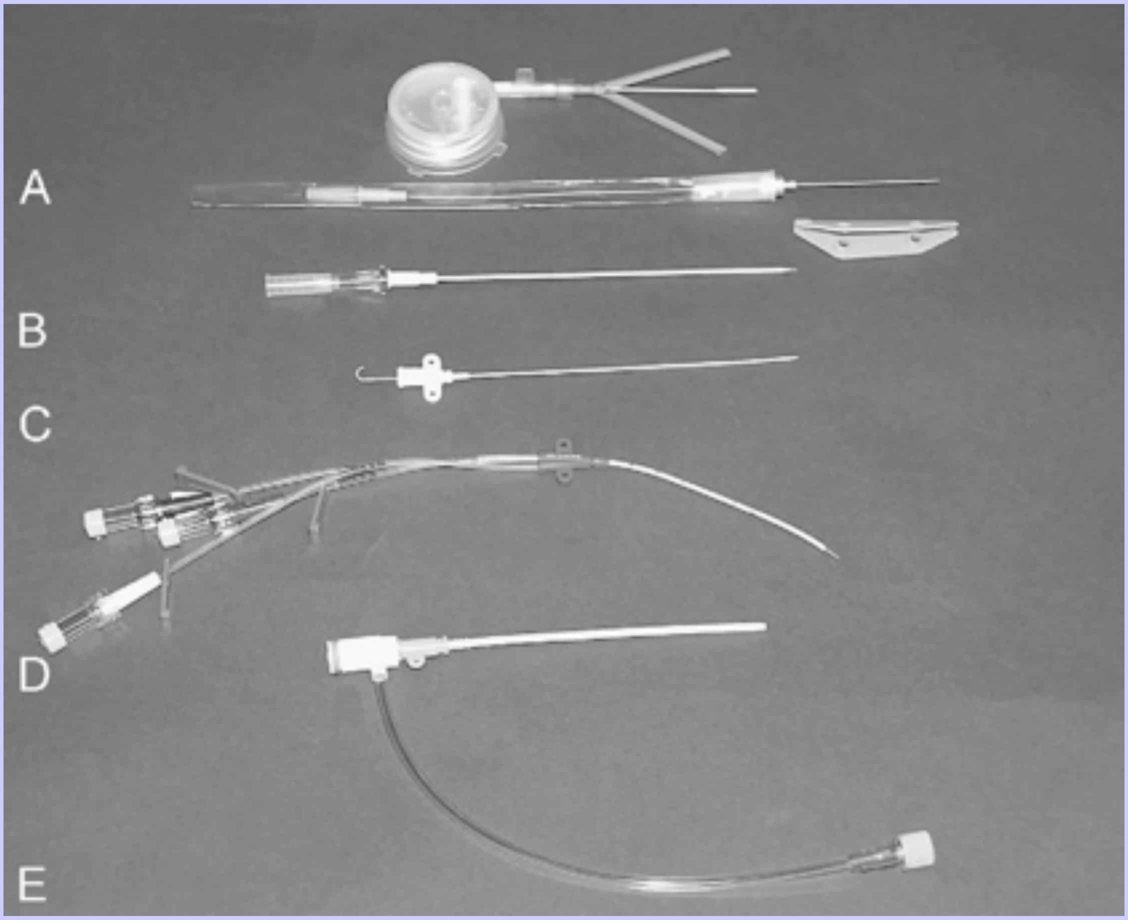
63.4.2 Over-the-Needle

Over-the-needle catheters were discussed in Chapter 61, Peripheral Venous Catheterization. When used for jugular catheterization, they must be of a length appropriate for the patient's size. The subcutaneous tissues in the region of the jugular vein are very loose, resulting in a lot of skin movement. Even though the catheter is well secured to the skin, short catheters can be pulled out of the vein easily.

63.4.3 Long Single-Lumen Catheter

This type of catheter is inserted using the Seldinger guidewire technique or a peel-off sheathed needle technique.[2] These catheters come in a variety of sizes and lengths. Mila International (Florence, KY) and Arrow International (Reading, PA) make central venous catheters that are 14 or 16 gauge by 6 or 8 inches (15 or 20 cm, respectively). Arrow also makes a 20-gauge by 5-inch (12 cm) and a 22-gauge by 4-inch (10 cm) single-lumen catheter. SurgiVet (Waukesha, WI) makes 5, 6, 7, and 8 Fr central venous catheters; the 5 Fr is 6 inches (15 cm) in length and all others are 10 inches (25 cm).

Figure 63-1 Examples of catheters used for central venous catheterization. **A,** Examples of two through-the-needle catheters; the top catheter is a Drum-Cartridge and the other is an Intracath. **B,** A long over-the-needle-catheter. **C,** Central venous catheter. **D,** Triple-lumen catheter. **E,** Catheter sheath introducer.



63.4.4

Multilumen Catheters

Multilumen catheters are placed using the Seldinger guidewire technique or a peel-off sheathed needle technique. Mila and Arrow make multilumen catheters. The catheters may be double, triple, or quadruple lumen. They are available in sizes ranging from 4 to 8.5 Fr and 2 to 24 inches (5 to 60 cm) in length.

Multilumen catheters are extremely useful in the critical care setting; they reduce the number of catheters that need to be placed in the critically ill patient. Fluids and drugs that are incompatible can be administered simultaneously. The catheters can be purchased individually or as a kit that contains all the components necessary for insertion. In addition to the catheter and dilators, the kits include local anesthetic, scalpel, syringe, and so on. Multilumen catheters are more expensive than the commonly used single-lumen catheters.

63.4.5 Percutaneous Sheath Catheter Introducer

Percutaneous sheath introducer systems are large-bore (typically 6 to 8 Fr), relatively short (4 inches) catheters that have a hemostasis valve located in the hub. They also have a short T-extension port for the fluid administration. A central venous catheter, pulmonary artery catheter, or transvenous pacing lead can be passed through the hemostasis valve into the jugular vein. The hemostasis valve acts as a seal to prevent entry of air into the circulation as well as to prevent blood or fluid loss around the catheter. The introducer must be placed with the Seldinger guidewire technique.

63.5 CATHETER INSERTION SITE

Central vein insertion sites include the jugular vein and the lateral and medial saphenous veins (see Chapter 61, Peripheral Venous Catheterization). Long catheters theoretically can be inserted in the cephalic vein and passed up to the level of the cranial vena cava, but they frequently will not pass beyond the elbow. For this reason the cephalic vein rarely is used for PICC lines.

63.5.1 Saphenous Vein

To achieve central vein catheterization via the saphenous vein, long catheters must be used; they are threaded so that they lie in the caudal vena cava. In dogs the lateral saphenous vein is used most commonly, but the medial saphenous vein can also be catheterized. In cats the medial saphenous vein tends to be larger and more easily stabilized for catheterization.

63.5.2 Jugular Vein

The jugular vein is catheterized directly in the cervical region. It lies along a line drawn between the angle of the mandible and the thoracic inlet. Jugular vein catheterization is feasible in both dogs and cats, and the vein may be visible in hemodynamically unstable patients when peripheral venous access is challenging.

The key to jugular catheter insertion is patient positioning and vessel immobilization. If the patient is not positioned properly it can be difficult to visualize and immobilize the vein. Jugular catheters are placed 268 antegrade, with the tip of the catheter always directed toward the heart. Placement of the jugular catheter is best 269 done with the patient in lateral recumbency. The patient's head is extended and its forelimbs positioned caudally by an assistant. Sedation of uncooperative patients is recommended. A bag of fluid, a sandbag, or rolled towels placed under the neck may be helpful (Color Plate 63-1). This flexes the neck and helps to make the vessel more accessible. The assistant should hold off the vein by pressing into the thoracic inlet; this should cause the vein to engorge and “stand up.” The other end of the vein is immobilized by extending the head.

In some cases venous cutdown may be needed to facilitate placement of a central catheter (see Chapter 61, Peripheral Venous Catheterization).

63.6 CATHETER INSERTION

Strict aseptic technique is followed for all central venous catheterization. Sterile gloves should be worn and the insertion site draped if the Seldinger technique is used or if the catheter will be used for total parenteral nutrition.

63.6.1 Through-the-Needle Catheter

The catheter needle should be introduced subcutaneously. The needle tip is positioned over the vein and aligned as close as possible to the longitudinal axis of the vein. The needle tip is inserted into the vein; it maybe necessary to angle the needle somewhat in order to pick up the superficial vein wall. Once it is estimated that the entire needle tip is within the lumen of the vein, the needle is stabilized and the catheter is threaded into the vein. Once the catheter is fully advanced into the vein, apply pressure over the venous puncture site and back the needle out. Once the bleeding has stopped, secure the needle guard around the needle. The catheter is aspirated to confirm proper placement and to clear it of air. It is then flushed with heparinized saline. The catheter should be capped with an injection cap or T-port and flushed again with heparinized saline. The catheter is sutured or stapled close to the insertion site. The insertion site is then covered with a sterile 2 × 2 gauze pad and the catheter site is bandaged.

An alternative insertion of the through-the-needle catheter is to remove the long single-lumen catheter from the insertion needle provided and thread it through a short over-the-needle catheter instead. Appropriate aseptic technique is maintained. This is particularly useful for placing PICC lines in saphenous vessels of small patients. The large needle provided with these catheters is commonly too large for effective venipuncture of a peripheral vessel. Using an over-the-needle catheter as an introducer makes initial venipuncture relatively simple, and the through-the-needle catheter is generally more affordable than a multilumen catheter.

In this situation, a common approach is to first insert a short over-the-needle catheter into the medial or lateral saphenous vein (Color Plate 63-2, *A*). A through-the-needle catheter (with the needle removed) is advanced into the preplaced catheter (Color Plate 63-2, *B*). The two catheter hubs are joined tightly together (Color Plate 63-2, *C*). Butterfly wing tape is used at the catheter hub juncture to prevent accidental dislodgement. The tape is sutured to the catheter (to prevent the tape from slipping) and the tape wings are sutured to the skin proximally to pull the catheter back toward the insertion site (Color Plate 63-2, *D*).

63.6.2 Seldinger Technique

The Seldinger technique uses a smaller introducing catheter or trochar and a guidewire to gain access to vessels or hollow organs. It avoids the requirement of initially puncturing the vessel with a large-bore catheter or trochar.[3] It maybe used to place single-lumen catheters, multilumen catheters, or percutaneous catheter introducer systems. It can also be used to replace an existing catheter in the same location. The Seldinger technique for introduction of a multilumen catheter is described here. The basic concept of this technique will be the same for any type of catheter placement in any vessel.[3]

Before beginning the procedure, the required distance for catheter insertion is premeasured. The aim for a jugular catheter is to have the tip lying within the thoracic cavity, just cranial to the right atrium. This distance commonly is estimated by measuring the distance from the intended insertion site to the caudal edge of the triceps muscle or first rib. For PICC lines the distance from the insertion site to the vena cava is measured. These measurements will then aid in choosing the most appropriate catheter for that patient.

The insertion site is clipped widely and surgically prepared in a routine manner.[1] Infiltration of the intended insertion site with local anesthetic is recommended in conscious animals. The catheter kit, sterile gauze, scalpel blade, suture material, and instruments are opened on a sterile field. The operator wears sterile gloves; in some circumstances a hat, mask, and sterile gown may also be appropriate, and an assistant can be helpful in challenging cases. The distal port of the multilumen catheter is identified. This is the port that terminates at the very tip of the catheter and will be the one through which the guidewire is passed. All ports of the multilumen catheter are flushed with heparinized saline and all ports, with the exception of the distal port, are capped. The insertion site is draped; this is important because the guidewire is long and flimsy, and the risk for contamination is high if draping is not sufficient.

A small relief incision is made through the dermis with a scalpel blade at the site of intended insertion. The introducing needle or short over-the-needle catheter (Color Plate 63-3, *A*) enters the skin through the relief incision and is inserted into the underlying vessel. The guidewire is threaded through the inserting needle or catheter into the vein (Color Plate 64-3, *B*). The distal end of the wire has a flexible J-tip to prevent puncturing the vessel wall. In some instances when it is difficult to pass the J-tip along the vessel, it maybe advantageous to use the straight end of the guidewire instead. It is important to recognize that this will be more traumatic to the vessel and that gentle technique should be maintained at all times. To prevent embolism of the guidewire, the operator should keep hold of it at all times.

Once the guidewire is inserted, approximately two thirds to three fourths of its length is fed into the vessel. It is held in place while the introducing needle or catheter is removed and a vessel dilator is threaded over the wire. The skin entry site may need to be enlarged with a No. 11 scalpel blade to accommodate the dilator. The dilator is grasped near the distal tip and, using a forward twisting motion, is advanced into the vessel (Color Plate 63-3, *C*). To minimize blood loss, pressure is applied over the insertion site with sterile gauze pads as the dilator is removed, leaving the guidewire in place.

In the case of a sheath introducer, the dilator is incorporated in the sheath and is removed once the sheath is in place. The multilumen catheter is threaded over the guidewire until the proximal end of the guidewire protrudes from the hub of the catheter. If the guidewire was advanced too far into the vessel, it will be necessary to back it out of the vessel to achieve this. Finally, while the proximal end of the guidewire is held, the catheter is advanced into the vessel the desired distance as determined by previous measurement (Color Plate 63-3, *D*). The wire is removed.

All ports are then aspirated to remove any air and to ensure that blood is easily drawn through the catheter. If necessary the catheter may be repositioned to allow aspiration of blood. Aseptic technique must be maintained throughout. All ports are flushed with heparinized saline. The catheter is then sutured in place; the insertion site is covered with sterile gauze and bandaged appropriately.

63.6.3 Peel-Off Sheathed Needle Technique

The peel-off sheathed needle (Mila International and SurgiVet) is similar to an over-the-needle catheter. The sheath has two tabs on the proximal end near the hub of the needle; when the tabs are pulled the sheath will split or peel away. The peel-off sheath technique can be used to place long single-lumen and multilumen catheters.

Peel-off sheath placement is similar to over-the-needle catheter technique. Once the needle and sheath placement is confirmed by bleeding, the needle is removed leaving the sheath in the vessel. The catheter is threaded down the sheath. The sheath is then peeled apart by grasping the tabs and pulling outward and upward. Once the sheath is completely separated, the catheter is positioned and secured.

63.7 COMPLICATIONS AND CATHETER MAINTENANCE

The same complications and catheter maintenance as discussed in Chapter 61, Peripheral Venous Catheterization, apply to central venous catheters (see Chapter 116, Catheter-Related Bloodstream Infection).

63.7.1 Heparinized Saline

All unused ports on central venous catheters should be flushed with heparinized saline. The author uses 4 U/ml of heparinized saline (1000 U/250 ml normal saline) q4h. Bags of heparinized saline should be discarded every 12 to 24 hours to minimize the risk of contamination. If a catheter port is not going to be used for a prolonged period, an alternative is to use a heparin lock. The dead space of the catheter is filled with 100 U/ml heparin q12h. The concentrated heparin solution is never flushed into the patient; instead, it is aspirated before administering medications or before replacing the heparin lock. Clear labeling of such ports to avoid inadvertent flushing of the concentrated heparin into the patient is important.

63.8 SUGGESTED FURTHER READING*

MW Beal: Placement of central venous catheters: Seldinger technique. In *NAVC Clinician's Brief*. 2005, Oct 7-10 *An excellent review of the Seldinger technique with step-by-step photographs*.

B Hansen: Technical aspects of fluid therapy. In SP DiBartola (Ed.): *Fluid, electrolyte and acid-base disorders in small animal practice*. 2006, Saunders, St Louis, *Fluid therapy chapter that includes a discussion of catheter selection and placement techniques with an excellent discussion of skin preparation for venous catheterization*.

RN White: Emergency techniques. In L King, R Hammond (Eds.): *Manual of canine and feline emergency and critical care*. 1999, British Small Animal Veterinary Association, Cheltenham, *Review of most catheterization techniques, including peripheral and central venous catheters*.

* See the CD-ROM for a complete list of references

64 Chapter 64 Daily Intravenous Fluid Therapy

Deborah C. Silverstein, DVM, DACVECC

64.1 KEY POINTS

- Daily intravenous fluid therapy is used to correct dehydration, provide maintenance fluid and electrolyte needs, and replace ongoing losses.
- The movement of fluid within the body is determined by hydrostatic pressure, colloid osmotic pressure, vascular endothelial permeability, and osmolality.
- Total body water is distributed in the intracellular and extracellular (plasma and interstitium) fluid compartments. The intracellular space is much larger than the extracellular space.
- The most common types of daily intravenous fluids include isotonic crystalloids, hypotonic crystalloids, free water solutions, and synthetic colloids.
- The fluid type and rate should be tailored to the individual patient's needs.
- Potential complications of fluid therapy include pulmonary edema, subcutaneous edema, organ edema, and electrolyte imbalances.

64.2 INTRODUCTION

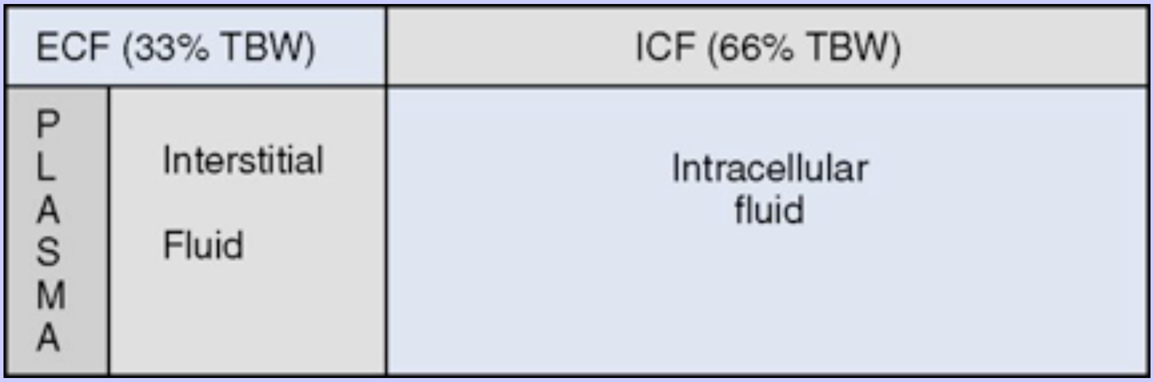
Intravenous fluid therapy is vital for the management of shock, dehydration, and maintenance in animals that require parenteral fluid therapy (see Chapters 61, 62, and 63, Peripheral Venous Catheterization, Intraosseous Catheterization, and Central Venous Catheterization, respectively, and Chapters 65 and 66, Shock Fluids and Fluid Challenge and Transfusion Medicine, respectively). This chapter focuses primarily on the distribution of total body water, patient assessment, and the delivery of synthetic intravenous fluids to maintain normal water, electrolyte, and acid-base status in critically ill dogs and cats that are hemodynamically stable. Because critically ill animals often have fluid and electrolyte balance derangements, overall recovery often depends on recognition and appropriate treatment of these disorders, in addition to diagnosing and treating the primary disease process.

64.3 TOTAL BODY WATER

Living organisms are predominantly composed of water. Total body water content is approximately 60% of body weight in a nonobese adult dog or cat. Total body water is distributed between two main compartments: intracellular fluid (ICF) and extracellular fluid (ECF) (Figure 64-1). Each compartment consists of solutes, primarily electrolytes, dissolved in water. The most important determinant of the size of each body fluid compartment is the quantity of solutes contained in that compartment.[1,2]

The ICF compartment is the larger of the two and comprises 66% of the total body water and 40% of body weight. It is separated from the ECF compartment by the cell membrane, which is very permeable to water but impermeable to most solutes. Cell membranes contain numerous proteins, including ion channels and active solute pumps. The most important active pump is the sodium-potassium ATPase pump, which extrudes three sodium ions out of the cell in exchange for bringing two potassium ions into the cell. This pump is responsible for generation of the electrochemical gradient across cell membranes, typified by a high intracellular potassium concentration, high extracellular sodium concentration, and a negative resting membrane potential.Therefore the most prevalent cation in the ICF is potassium, with much smaller contributions made by magnesium and sodium. The most prevalent anions in the ICF are phosphate and the polyanionic charges of the intracellular proteins.[1,2]

Figure 64-1 The distribution of total body water *(TBW). ECF,* Extracellular fluid; *ICF,* intracellular fluid.



The ECF comprises the remaining 33% of the total body water and 20% of body weight. The ECF is subdivided into the plasma (25% of ECF) and interstitial (75% of ECF) fluid compartments. The interstitial fluid bathes all cells and includes lymph. The primary cation in the ECF is sodium and the most prevalent anions are Cl^- and HCO_3^-. The proteins in plasma and the interstitial space also contribute to the negative charges. The oncotic pressure gradient between the intravascular and interstitial spaces is determined by the ratio of proteins in these two compartments.[1,2]

64.4 MOVEMENT OF FLUIDS WITHIN THE BODY

Water moves freely within most compartments in the body. Small particles such as electrolytes move freely between the intravascular and interstitial compartment, but cannot enter or leave the cellular compartment without a transport system. Larger molecules (>20,000 daltons) do not easily cross the vascular endothelial membrane and may attract small, charged particles, thus creating the colloid osmotic pressure (COP). There are three main natural colloid particles: albumin, globulins, and fibrinogen. An increase in the pressure of fluid within a compartment that pushes against a membrane is known as *hydrostatic pressure*.

In health, fluid balance is determined by the balance between forces that favor reabsorption of fluid into the vascular compartment (increased COP or decreased hydrostatic pressure) and those that favor filtration out of the vascular space (decreased COP or increased hydrostatic pressure).[1] Changes in the osmolality between any of the fluid compartments within the body will cause free water movement across the respective membrane. 271 272

In disease states, both increased fluid losses and decreased intake may lead to dehydration. The nature of the fluid loss (hypotonic, isotonic, or hypertonic) will determine the subsequent changes in osmolality. This will in turn dictate the relative impact on the ICF and ECF compartments.

64.4.1 Isotonic Fluid Loss

Isotonic fluid losses, as seen in animals with polyuric renal failure or bleeding, will lead to depletion of the ECF compartment and dehydration. If severe ECF losses are not replaced, hypovolemia may become clinically apparent. Because isotonic losses will not alter ECF osmolality, there will be no movement of water across the cell membrane and ICF volume will remain unchanged. In order to replace the ECF deficit, isotonic crystalloids should be administered (see Fluid Deficit).

64.4.2 Hypotonic Fluid Loss

Hypotonic fluid losses, as seen with diabetes insipidus or excessive panting, will cause hypernatremia and an increase in ECF osmolality. This will lead to movement of water out of the ICF space. Consequently, there is a depletion of both the ICF and ECF compartments. Isotonic fluid therapy may be sufficient if the hypernatremia is not severe, but in animals with significant hypotonic fluid losses, free water administration is indicated. Care must be taken to lower serum sodium slowly to avoid causing potentially life-threatening cerebral edema (see Chapter 54, Sodium Disorders).

64.4.3 Hypertonic Fluid Loss

Loss of hypertonic fluid, such as with heat exhaustion or highly concentrated urine, may cause hyponatremia and hypoosmolality. This maybe a direct result of the loss of high solute–containing fluid or may be exacerbated by a combination of isotonic or hypertonic fluid loss with hypotonic fluid replacement (i.e., oral water intake). Hypoosmolality will lead to water movement into the ICF compartment, resulting in dehydration and intracellular edema. Significant hyponatremia or hypoosmolality will require careful fluid therapy to avoid rapid (>0.5 mEq/L increase per hour) changes in sodium concentration and subsequent central pontine myelinolysis.

64.4.4 Increased Vascular Permeability

Disease processes that cause an increase in vascular permeability may lead to high-protein fluid extravasation from the intravascular space. This can lead to a decrease in intravascular volume, possibly associated with interstitial edema. Because this will not alter the osmolality of the ECF compartment, increased vascular permeability alone is not expected to alter the ICF volume.

Patient history, physical examination, and laboratory data can provide useful information concerning the route of fluid losses, timeline of these losses, food and water consumption, and current clinical status. This will guide formulation of an appropriate fluid therapy plan.

64.5 FLUID THERAPY PLAN

The fluid type and rate of administration chosen depend primarily on the clinical status of the animal based on the physical examination and laboratory parameters. For animals with evidence of chronic dehydration on physical examination, but stable cardiovascular parameters, fluid deficits should be replaced over 4 to 24 hours. Isotonic replacement fluids are administered according to the patient's estimated dehydration, maintenance needs, and anticipated ongoing losses.

To determine the quantity of fluid necessary for the stable patient with evidence of dehydration, the following formula is used:

$$\begin{aligned}&\text{Body weight (g)} \times \text{percentage dehydration (} = \text{deficit)}\\&\qquad + \text{estimated ongoing losses (ml)}\\&\qquad + \text{maintenance (ml)}\\&= \text{amount to be given (ml) over next } 4 \text{ to } 24 \text{ hours}\end{aligned}$$

64.5.1 Fluid Deficit

Volume deficiencies in each of the body fluid compartments exhibit different clinical signs or laboratory abnormalities. ICF deficits lead to cerebral obtundation, hypernatremia, and hyperosmolality. ICF deficits alone will not cause clinical evidence of dehydration. In contrast, interstitial volume deficits typically are associated with a decrease in skin turgor (increased skin tenting) and dry mucous membranes. Skin turgor provides only a rough estimate of dehydration, and severe emaciation or obesity can make this assessment difficult. Intravascular volume deficits commonly are associated with compensatory vasoconstriction, pale mucous membranes, poor pulse quality, tachycardia, prolonged capillary refill time, and cold extremities. These symptoms are suggestive of poor tissue perfusion and require rapid intervention. Physical examination findings in animals with evidence of dehydration are listed in Table 64-1.

64.5.2 Maintenance

Daily maintenance fluid needs have not been well studied in the dog and cat, so it is especially important that 272
animals receiving intravenous fluids be assessed several times per day. The formula most commonly used is 273
$(BW_{kg} \times 30) + 70$ (ml per day). For animals that weigh less than 2 or more than 50 kg, an alternative formula should be used: $(BW_{kg}{}^{0.75})70$. These calculations take into account the sensible and insensible ongoing fluid losses (feces, urine, panting, sweating). Because there is less water in fat than in muscle, these calculations will overestimate the maintenance needs of overweight patients.[3,4]

Table 64-1 Physical Examination Findings in Dehydrated Patients

Percentage of Dehydration	**Clinical Signs**
<5	No detectable abnormalities
5 to 8	Decreased skin turgor, dry mucous membranes
8 to 10	Decreased skin turgor, dry mucous membranes, eyes may be sunken in orbits, slight prolongation of CRT
10 to 12	Severe skin tenting, prolonged CRT, dry mucous membranes, eyes sunken in orbits, possibly signs of shock
12	All of the above plus signs of shock, often life threatening

CRT, Capillary refill time.

64.5.3 Ongoing Losses

Ongoing fluid losses are estimated from an understanding of the underlying disease process and historical data. For example, when treating animals with gastrointestinal losses the approximate volume and frequency of vomiting and diarrhea is estimated. Obviously this predicted volume may be inaccurate; it allows calculation of an initial fluid therapy plan, but close patient monitoring and reevaluation are imperative. If the estimate of ongoing fluid losses is significantly inaccurate, the fluid plan should be altered accordingly.

64.5.4 Route of Administration

Although subcutaneous fluid administration can be effective in the management of fluid deficits, it is not adequate for the critically ill patient. Fluid therapy should be administered via an intravenous catheter that is checked regularly for evidence of phlebitis or inadvertent subcutaneous fluid administration.

64.6 FLUID TYPE

The type of fluid that should be administered depends on the individual patient. Options for the critically ill patient include replacement fluids, maintenance fluids, free water solutions, and synthetic colloids.

64.6.1 Replacement Fluids

Replacement fluids, also known as *isotonic crystalloids,* are electrolyte-containing fluids with a composition similar to that of the ECF. They have the same osmolality as plasma (290 to 310 mOsm/L); the electrolytes are small in size, and they do not significantly change the osmolality of the vascular or extravascular space in animals with a normal osmolality.[4,5] They may also contain acid-base components and dextrose. Isotonic crystalloids are commonly used to expand the intravascular and interstitial spaces and maintain hydration. The constituents of commonly used isotonic fluids can be found in Table 64-2. Additional electrolytes, such as potassium, may be added to maintenance or replacement fluids as needed for an individual patient (see Part V, Electrolyte and Acid-Base Disturbances).

Following infusion of isotonic crystalloids into the vascular space, the small electrolytes and water pass freely across the vascular endothelium. These fluids are extracellular-expanding fluids; 75% redistributes to the interstitial space, and only 25% remains in the vascular space after 30 minutes.[6] Although so-called *replacement fluids* are used commonly for maintenance of hydration, most animals are able to easily excrete the electrolyte constituents that are in excess of the body's needs. This practice is common, because most hospitalized animals have ongoing electrolyte losses and poor enteral intake, and it is much easier to hang one bag of isotonic crystalloids than two separate bags (one for replacement and one for maintenance). The rate of fluid replacement is determined as outlined earlier in this chapter.

Not all isotonic fluids are created equal, as seen in Table 64-2. Isotonic saline solution (0.9% NaCl) contains a higher concentration of sodium and chloride (154 mEq/L of each) than does normal blood, and will cause proportional changes (increases) in the recipient electrolytes. Therefore large amounts of 0.9% NaCl will cause a mild increase in serum sodium, a marked increase in chloride, and a moderate decrease in bicarbonate and potassium. The kidneys typically will compensate, if possible, by excreting the excess electrolytes and conserving potassium.

Isotonic crystalloids can cause harm, especially in critically ill animals. The interstitial fluid gain can lead to interstitial edema, pulmonary edema, and cerebral edema. Patients with a low COP, pulmonary contusions, cerebral trauma, fluid-unresponsive renal disease, or cardiac failure are at highest risk for complications. In addition, substantial hemodilution of blood constituents that are not found in the crystalloids can occur. Anemia, hypoproteinemia, and hypocoagulability can occur following large-volume crystalloid administration.

Although all isotonic crystalloids have a similar composition, there are situations in which a specific fluid type may be preferable over another. Specifically, animals with diabetic ketoacidosis or liver disease should not receive lactate-containing fluids because of their decreased ability to convert the lactate to bicarbonate in the liver. However, lactated Ringer's solution may be preferred in very young animals because lactate is the preferred metabolic fuel in neonates with hypoglycemia. Patients with a hypochloremic metabolic alkalosis will benefit from 0.9% sodium chloride, because this is the highest chloride-containing fluid, but animals with a severe acidosis may benefit from an alkalinizing fluid containing lactate, acetate, or gluconate (see Table 64-2). Animals with head trauma or increased intracranial pressure may benefit from 0.9% sodium chloride, because this isotonic crystalloid is least likely to cause a decrease in osmolality that might promote water movement into the brain interstitium.

64.6.2 Maintenance Fluids

Maintenance fluids refer to the volume of fluid and amount of electrolytes that must be consumed on a daily basis to keep the volume of total body water and electrolyte content within the normal range. Obligate fluid losses are hypotonic and hyponatremic, but contain relatively more potassium than does the ECF.[7] Maintenance fluids are therefore hypotonic crystalloids that are low in sodium, chloride, and osmolality, but high in potassium compared with normal plasma concentrations (Table 64-3). The inclusion of dextrose may make the fluid isoosmotic to plasma, but the dextrose is metabolized rapidly to carbon dioxide and water, so these fluids are still hypotonic in nature. As mentioned earlier, daily maintenance needs are calculated as $(BW_{kg} \times 30) + 70$ (mL per day). For animals that weigh less than 2 or more than 50 kg, an alternative formula should be used: $(BW_{kg}^{0.75})70$. Maintenance-type fluids are distributed into all body fluid compartments and should never be administered as a bolus or cerebral edema may result.

Table 64-2 Isotonic Crystalloid Compositions

Fluid Type	Osmolality	$[Na^+]$ (mEq/L)	$[K^+]$ (mEq/L)	$[Cl^-]$ (mEq/L)	$[Mg^{++}]$ (mEq/L)	$[Ca^{++}]$ (mEq/L)	Lactate (mEq/L)	Acetate (mEq/L)	Gluconate (mEq/L)
0.9% NaCl	308	154	—	154	—	—	—	—	—
Lactated Ringer's solution	273	130	4	109	—	3	28	—	—
Plasmalyte 148	295	140	5	98	3	—	—	27	23
Normosol-R	295	140	5	98	3	—	—	27	23

Table 64-3 Maintenance and Free Water Solution Compositions

Fluid Type	Osmolality	$[Na^+]$ (mEq/L)	$[K^+]$ (mEq/L)	$[Cl^-]$ (mEq/L)	$[Mg^{++}]$ (mEq/L)	$[Ca^{++}]$ (mEq/L)	Lactate (mEq/L)	Acetate (mEq/L)	Dextrose
0.45% NaCl	150	77	0	77	—	—	—	—	—
0.45% NaCl with 2.5% dextrose	203	77	—	77	—	—	—	—	2.5%
Plasmalyte 56	110	40	13	40	3	—	—	16	—
Normosol-M	110	40	13	40	3	—	—	16	—
1/2 LRS with 2.5% dextrose	265	130	4	109	—	3	28	—	2.5%
D5W	252	—	—	—	—	—	—	—	5%

D5W, 5% dextrose in water; *LRS,* lactated Ringer's solution.

64.6.3 Free Water Administration

In order to give free water (fluids with no electrolytes or buffers) intravenously without using a dangerously hypotonic fluid, the water is combined with 5% dextrose to yield an osmolality of 252 mOsm/kg (safe for intravenous administration). This fluid is indicated in animals with a free water deficit (i.e., hypernatremia) or severe ongoing free water losses (i.e., diabetes insipidus). In order to safely lower the sodium concentration by 1 mEq/hr, a rate of 3.7 ml/kg/hr is a good starting point and can be adjusted based on the patient's response. Close monitoring of electrolyte status is advised. Dextrose 5% in water should never be administered as a bolus because acute decreases in osmolality will cause potentially fatal cerebral edema.

64.6.4 Synthetic Colloids

The most commonly used synthetic colloid solutions include dextran-70 and hydroxyethyl starch (hetastarch). Colloids are large molecules (molecular weight >20,000 daltons) that do not readily sieve across the vascular membrane. The base solution of most products is 0.9% sodium chloride, and the colloidal particles are suspended within the crystalloid. These fluids are polydisperse (they contain molecules with a variety of molecular weights) and hyperoncotic to the normal animal, and therefore cause the movement of fluid from the extravascular to the intravascular space. Synthetic colloids lead to an increase in blood volume that is greater than that of the infused volume and also aid in the retention of this fluid in the vascular space (in animals with normal capillary permeability). Dextran-70 is a 6% colloidal solution with particles that range from 15,000 to 3,400,000 daltons, a number average molecular weight of 41,000, and a COP of 60 mm Hg in vitro. Hetastarch is also a 6% solution, with particles ranging from 10,000 to 1,000,000 daltons in molecular weight, a number average molecular weight of 69,000 daltons, and a COP of 34 mm Hg in vitro. Excessive volumes may lead to volume overload, coagulopathies, and hemodilution. Synthetic colloids typically are used in combination with isotonic crystalloids to maintain adequate plasma volume expansion with lower interstitial fluid volume expansion. Continuous rate infusions are commonly used at a rate of 0.5 to 2 ml/kg/hr in animals with acute decreases in COP or total protein levels.[7,8]

The use of fresh or stored whole blood, packed red blood cells, or plasma products is often necessary in critically ill animals. A thorough discussion of transfusion medicine can be found in Chapter 66.

64.7 MONITORING

Animals receiving intravenous fluids should be monitored closely. Body weight should be monitored daily (or more often if indicated) and a physical examination should be performed at least twice daily to assess the animal's mental status, skin turgor, heart rate and pulse quality, mucous membrane color, capillary refill time, extremity temperature, and respiratory rate and effort. Serial lung auscultation should be performed to monitor for increased breath sounds, crackles, or wheezes. Clinical signs in animals receiving too much fluid include serous nasal discharge, chemosis, jugular venous distention, and interstitial pitting edema. In the early stages of pulmonary edema, an increase in the respiratory rate will occur, followed by inspiratory crackles, wheezes, and dyspnea. It is therefore of utmost importance to monitor the respiratory rate and effort of all patients receiving fluid therapy.

If an indwelling urinary catheter is present, urine output can be compared with fluid input to help guide fluid 274
therapy and prevent the administration of too much or too little fluid. Serum blood urea nitrogen and creatinine 275
levels can be evaluated in conjunction with the urine specific gravity to determine whether there is prerenal or renal azotemia (or a combination of both). An increase in blood urea nitrogen and creatinine with an increase in urine specific gravity would suggest that the animal is receiving insufficient fluid volume. Inadequate tissue perfusion may result in an increase in blood lactate levels secondary to anaerobic metabolism. Serial lactate measurements may help guide fluid therapy as an indicator of tissue perfusion. Moderate to severely elevated lactate levels should alert the clinician that more aggressive treatment may be required.

If a central venous catheter is in place, central venous pressure monitoring may be used to help guide fluid therapy. Although this is a measurement of the pressure in the vena cava, it is used commonly to evaluate volume, because there is normally a direct relationship between the two parameters (see Chapter 203, Hemodynamic Monitoring). Additional monitoring techniques that might be helpful include arterial blood pressure, electrocardiogram, and repeated measurements of packed cell volume, total solids, blood glucose, electrolytes, and acid-base status. An increase in the activated partial thromboplastin time (APTT) may develop in animals that receive large amounts of synthetic colloid therapy, although the quantitative APTT change is not predictive of clinical bleeding. Coagulation times should be monitored and transfusion therapy initiated as needed. Pulmonary capillary wedge pressure monitoring, cardiac output monitoring, and mixed venous oxygen saturation measurements may be helpful in select patients.

64.8 DISCONTINUATION OF FLUID THERAPY

In most animals, fluid therapy should not be discontinued abruptly, especially if high flow rates are being administered. These animals may have renal medullary washout and therefore the urine concentrating ability will be impaired for several days. This can lead to severe dehydration and hypovolemia in animals that are not drinking large amounts of water. Ideally, intravenous fluid therapy should be decreased gradually over a 24-hour period. Some animals may require slower weaning protocols, especially those receiving high flow rates. Owners should be informed that the animal may have increased water requirements for a few days after the discontinuation of intravenous fluid therapy.

In conclusion, intravenous fluid therapy should be used to maintain normal water, electrolyte, and acid-base status in dogs and cats that are hemodynamically stable. The fluid plan should be tailored to the animal's state of hydration, continued maintenance needs, coexisting diseases, laboratory abnormalities, and anticipated ongoing losses. Critically ill animals commonly require intravenous fluid therapy, and an understanding of body fluid compartments and the distribution of various fluid types is essential when formulating a treatment strategy. Judicious monitoring is vital, and a gradual weaning from fluid therapy is recommended.

64.9 SUGGESTED FURTHER READING*

SP DiBartola: In *Fluid, electrolyte and acid-base disorders in small animal practice*. ed 3, 2006, Saunders, Philadelphia, *A thorough and detailed fluid therapy and electrolyte/acid-base textbook for small animal veterinarians*.

DS Greco: The distribution of body water and general approach to the patient. *Vet Clin North Am Small Anim Pract*. **28**, 1998, 473, *A nice review of water composition in the small animal patient and practical guide for fluid therapy based on these concepts*.

R Kirby, E Rudloff: The critical need for colloids: maintaining fluid balance. *Comp Cont Ed Pract Vet*. **19**, 1997, 705, *This review paper provides a clear overview of use of colloid therapy in animals and the various products available*.

* See the CD-ROM for a complete list of references

65 Chapter 65 Shock Fluids and Fluid Challenge

Janet Aldrich, DVM, DACVECC

65.1 KEY POINTS

- The primary goal of shock therapy is to improve delivery of oxygen and other nutrients to metabolically active cells.
- Isotonic crystalloids and colloids, each at their appropriate dosages, are equally effective for managing shock. Hypertonic saline is usually combined with a colloid.
- Fluids should be chosen with consideration of concurrent conditions, such as dehydration, active bleeding, or brain injury.
- The fluid challenge technique is useful for hemodynamically unstable patients to determine if inadequate resuscitation is the cause of instability.

65.2 SHOCK

Circulatory shock refers to states of inadequate tissue perfusion causing the partial pressure of oxygen at the tissues to fall below a critical level required to maintain adequate energy production.[1] Circulatory shock can be further categorized as hypovolemic, cardiogenic, obstructive, or distributive in nature.[2] Hypovolemic shock is due to an absolute or relative reduction in blood volume. Cardiogenic shock describes inadequate tissue perfusion as a consequence of cardiac disease. Obstructive shock occurs when there is an obstruction such as an embolus or pericardial effusion impeding blood flow out of the heart or venous return to the heart. Distributive shock is due to inappropriate generalized vasodilation leading to inadequate perfusion. This is generally a consequence of systemic circulation of inflammatory mediators as can occur with the systemic inflammatory response syndrome or anaphylaxis.

The primary goal of shock therapy is to improve delivery of oxygen and other nutrients to metabolically active cells. Intravenous fluid therapy is essential in the resuscitation of patients with hypovolemic, distributive, and obstructive shock.[3,4] There may be a role for fluid therapy in some specific instances of cardiogenic shock, but it must be administered with caution and requires intensive monitoring (see Chapter 35, Cardiogenic Shock).

Fluids that are effective volume expanders in shock are isotonic crystalloids, hypertonic crystalloids, and synthetic colloids suspended in isotonic crystalloid solutions.

65.3 ISOTONIC CRYSTALLOIDS

The composition of isotonic (or nearly isotonic) crystalloid fluids is similar to that of extracellular fluid. They have sodium concentrations in the 130 to 154 mEq/L range and concentrations of other ions (potassium, magnesium, calcium) similar to those in extracellular fluids, and may contain bicarbonate-like anions (Table 65-1).

Table 65-1 Shock Fluid Dosage Ranges

	Total Shock Dosage*		**Fluid Challenge**	
Fluid Type	**Dogs**	**Cats**	**Dogs**	**Cats**
Isotonic crystalloids	80 ml/kg	50 ml/kg	20 ml/kg	10 ml/kg
Synthetic colloids	10 to 20 ml/kg	5 to 10 ml/kg	5 ml/kg	3 ml/kg
Hypertonic saline 7.5%	4 to 6 ml/kg	3 to 4 ml/kg	—	—
Hypertonic saline 7.5% combined with a synthetic colloid	4 to 6 ml/kg	2 to 4 ml/kg	—	—

65.3.1 Physiology

Rapid intravenous infusion of isotonic crystalloids causes continuous vascular volume expansion until the infusion stops, at which time most of the administered volume is in the vascular compartment. When 80 ml/kg was administered in 12 minutes to experimental, healthy dogs, blood volume was increased by 76% at the end of the infusion, 35% after 30 minutes, and 18% after 4 hours.[5]

Because of the fairly rapid distribution out of the vascular space, isotonic crystalloids must be administered at rapid rates to get the desired vascular volume expansion. Isotonic crystalloids have little effect on intracellular volume (see Chapter 64, Daily Intravenous Fluid Therapy).

* Shock fluid therapy should be given in increments and the total dosage determined by the individual response.

65.3.2 Benefits

Isotonic crystalloids are inexpensive, readily available, and have a long track record of success as resuscitation fluids. The redistribution to the interstitium is beneficial for many dogs and cats in shock, because their underlying problem often involves preexisting severe salt and water losses that have depleted the extracellular volume (dehydration).

65.3.3 Adverse Effects

If isotonic crystalloids are delivered too slowly, the desired vascular volume expansion is not achieved but 75% 276 of the administered volume is still distributed to the interstitium, predisposing the patient to interstitial fluid 277 overload, possibly to pulmonary edema. However, the lung is richly supplied with lymphatic vessels, which, among other factors, can protect it from interstitial fluid overload. Large-volume isotonic crystalloid resuscitation did not cause increases in lung water or hypoxemia in a canine hemorrhagic shock model.[6] Inappropriate and overzealous administration of isotonic crystalloids risks adverse effects of worsened pulmonary edema, increased intracranial pressure, and abdominal compartment syndrome.

Isotonic crystalloids dilute all plasma elements except those ions present in the administered fluid at plasma concentrations. Of major concern is dilution of albumin and therefore decrease in colloid osmotic pressure, and dilution of the red blood cell mass. With redistribution of crystalloid fluids this effect will be reduced.

Alterations in immunologic and proinflammatory states, such as neutrophil activation or increase in apoptosis, have occurred in experimental animals treated for shock with lactated Ringer's solution.[7-9] Pulmonary apoptosis was increased when the D isomer of lactate was substituted for L isomer in lactated Ringer's solution.[10] Intestinal hyperpermeability was decreased in an experimental hemorrhagic shock model when Ringer's ethyl pyruvate solution was used.[11]

65.3.4 Fluid Prescription

The estimated dosage of isotonic crystalloids for treating shock is equal to the patient's healthy blood volume (approximately 80 ml/kg for dogs, 50 ml/kg for cats). The actual fluid requirements of each patient will vary and must be prescribed individually. The total amount administered depends on the response to treatment and is usually one half to one blood volume (see Table 65-1). One strategy is to set up the fluid delivery system to deliver the prescribed amount in 20 minutes, and to slow or discontinue the infusion if the tissue perfusion parameters improve before the end of the infusion.

Pressure bags are helpful for rapid administration of large volumes of isotonic crystalloids. For cats, rapid infusion of fluids can be performed easily with a 60-ml syringe. This allows accurate measurement of the volume given and avoids the risk of inadvertent fluid overload. Patients are monitored continually throughout the resuscitation period, and rapid administration is stopped when the goals of resuscitation are accomplished.

65.4 COLLOIDS

Synthetic colloids (hydroxyethyl starch, dextran, gelatins) are isotonic crystalloid solutions to which large molecules have been added to achieve colloid concentrations of about 6%. Hydroxyethyl starch is available suspended in either isotonic saline (Hespan) or a solution similar to lactated Ringer's (Hextend). Dextran-70 is suspended in isotonic saline.

65.4.1 Physiology

Synthetic colloids redistribute into the interstitial space at a much lower ratio than the isotonic crystalloid fluids. They are expected to increase serum colloid osmotic pressure, which will lead to movement of fluid from the interstitial space into the vascular space. Consequently, colloid administration will increase blood volume by an amount greater than the infused volume. This means that effective resuscitation may be possible by administering smaller volumes. When the full dose of 20 ml/kg was administered in 5 minutes to experimental healthy dogs, blood volume was increased by 25% at the end of the infusion, 36% after 30 minutes, and 26% after 4 hours.[5] These fluids are isoosmotic, so there is little effect on intracellular volume (see Chapter 64, Daily Intravenous Fluid Therapy).

65.4.2 Benefits

Colloid solutions produce vascular volume expansion with less interstitial expansion than do crystalloid solutions. They support colloid osmotic pressure and are useful in patients who are symptomatic from their hypoalbuminemia. In theory, the larger molecular weight colloids, because of their molecular size and configuration, might seal capillary leaks in patients with capillary leak syndrome.[12] Some have postulated that capillaries have both small pores, which reflect colloids, and large pores, which do not. The capillary leak syndrome that occurs in critical illness causes a change in the number of these pores but not in their size. For this reason, the molecular weight distribution of hydroxyethyl starch would not be a determining factor.[13] Some studies have supported the benefits of colloids in capillary leak,[14,15] others have not.[13,16]

65.4.3 Adverse Effects

The most important adverse effect of synthetic colloids is on coagulation. High molecular weight hydroxyethyl starch (the only available formulation in the United States) and dextran at dosages greater than 20 ml/kg q24h are likely to prolong clotting times.[17-19]

The causes of these changes in coagulation are many, including decreases in factor VIII and von Willebrand factor. Clinically significant bleeding associated with these products is unpredictable, probably because concurrent disease affects coagulation in many critically ill patients. They should be used in caution with patients already showing blood clotting abnormalities or in those in which blood clotting ability is a major concern, such as in those undergoing emergency surgery.

Colloids dilute red blood cell mass and albumin, as do crystalloids, and this effect is long lasting in proportion to the persistence of colloids in the vascular space. Allergic reactions to hydroxyethyl starch, dextran, and gelatin are reported but are extremely rare.

65.4.4 Fluid Prescription

In anticipation that most of the administered volume will remain in the vascular space, and because of potential toxicity, the dosage of colloids is smaller than that of crystalloids. The usual volume for management of shock is 10 to 20 ml/kg for dogs and 5 to 10 ml/kg for cats (see Table 65-1). As described for isotonic crystalloid resuscitation, colloid administration should be titrated according to the individual patient's response. The total volume usually is administered over 5 to 10 minutes.

65.5 HYPERTONIC SALINE

The usual concentration of hypertonic saline used to treat shock is 7.2% to 7.5%. The approximate osmolality is 2400 mOsm/L.

65.5.1 Physiology

Hypertonic saline creates an osmotic gradient from the intracellular to extracellular fluid space, leading to a reduction in intracellular volume and an increase in extracellular volume. The recruited fluid distributes in the extracellular space according to the 1:3 vascular-to-interstitial ratio. Consequently the increase in intravascular volume is greater than the infused volume. When 4 ml/kg was administered over 5 minutes to experimental healthy dogs, the increase in blood volume was 17% at the end of the infusion, 12% after 30 minutes, and 3% after 4 hours.[5] These fluids are highly efficient, because they expand blood volume about 3.5 times the amount administered. However, because the volume infused is small the absolute increase in vascular volume is small.

65.5.2 Benefits

The small volume of hypertonic saline to be administered in shock makes it attractive for situations in which limited support is available, such as in prehospital resuscitation in humans. Hypertonic saline is an effective resuscitation fluid despite its relatively small impact on vascular volume in comparison with other fluids. Its effectiveness has been attributed to other physiologic benefits such as vasodilation, increased cardiac contractility, and immunomodulatory effects. Hypertonic saline causes arteriolar vasodilation and improved microcirculatory perfusion. This leads to improved regional blood flow of coronary, renal, and intestinal circulations.

There is contradictory evidence in the literature regarding the effect of hypertonic saline on cardiac contractility. Some reports describe a direct positive inotropic effect, and others attribute all hemodynamic benefits of hypertonic saline to a combination of volume expansion and decreased afterload. In one study, hypertonic saline was found to be a negative inotrope in normovolemic dogs. The effect of hypertonic saline on cardiac contractility in clinical veterinary patients remains unclear.

Experimental studies have found numerous immunomodulatory effects of hypertonic saline, including increases in cell-mediated immune function, reduced antiinflammatory cytokine production, inhibition of neutrophil activation,[20] and altered pulmonary macrophage activity. These findings have led to the suggestion that hypertonic saline may be beneficial in the resuscitation of victims of trauma and patients in septic shock, but randomized clinical trials evaluating this therapy are lacking.

Hypertonic saline can be beneficial for intracranial hypertension by virtue of its hypertonicity, and has been suggested to be the resuscitation fluid of choice for patients with traumatic brain injury.[21,22]

65.5.3 Adverse Effects

Hypernatremia always follows administration of hyper-tonic saline. If excessive volumes are administered or if the patient's effective osmolality is already high, the hypernatremia could be severe enough to cause neurologic signs of tremors, altered mentation, and seizures. At recommended dosages, the hypernatremia is not associated with clinical complications. Overly fast administration (>1 ml/kg/min) of hypertonic saline can cause bradycardia, hypotension, and bronchoconstriction.[23,24]

In patients with decreased reservoirs of intracellular volume, the efficacy of hypertonic saline may be diminished. But, in a hemorrhagic shock model of pigs previously dehydrated by 8% of their body weight, the hemodynamic response to resuscitation was maintained.[25] Hypertonic saline may dilate precapillary sphincters and alter distribution of blood flow.

65.5.4 Fluid Prescription

Hypertonic saline (7.5%) can be administered at a dosage of 4 to 6 ml/kg in dogs and 3 to 4 ml/kg in cats over approximately 5 minutes (see Table 65-1). Hypertonic saline often is combined with a colloid fluid, to prolong the volume-expanding effect.

65.6 FLUID COMBINATIONS

More than one fluid type may be used for shock fluid administration. Two common combinations are crystalloids with colloids and hypertonic saline with colloids.[26-28] The rationale of these combinations is to provide the immediate volume-expanding effects of crystalloids or hypertonic saline with the advantage of longer lasting vascular volume expansion of colloids. Crystalloid-colloid combinations have also been used in patients with hypovolemic shock and concurrent hypoproteinemia, as seen in diseases such as hemorrhagic gastroenteritis. The fluid dosage of a crystalloid-colloid combination is determined by response to therapy. Each fluid is given in increments as previously described and the patient's clinical response evaluated before further administration. When hypertonic saline–colloid combinations are given, they generally are used together and administered rapidly.[29] Dextran-70 is used most commonly in this protocol, but it could be replaced by hydroxyethyl starch. Proposed dosages for a solution of 7.5% saline in a colloid (dextran-70 or hydroxyethyl starch) are 4 to 6 ml/kg in dogs, and 3 to 4 ml/kg in cats. Again, response to therapy should be monitored and the low end of the dosage range used for cats (see Table 65-1).

65.7 CHOOSING A FLUID FOR TREATMENT OF SHOCK

The fluids described have distinctly different characteristics. Although most patients in shock can be resuscitated satisfactorily with any of them, certain patients are likely to benefit more from one fluid than another.

65.7.1 Preexisting Losses

Most preexisting volume losses in dogs and cats are a combination of salt and water in nearly isotonic 278 proportions (urinary or gastrointestinal losses) such that the patient has extracellular volume depletion with 279 normal or nearly normal effective osmolality. Thus intracellular volume is normal. These patients are usually described as dehydrated (de = loss, hydra = water), but the term is taken to mean loss of both salt and water. Isotonic crystalloids are the resuscitation fluid of choice because they replace vascular and interstitial volume deficits. Failure to repair the interstitial deficit puts the patient at risk of inadequate resuscitation and recurrent episodes of hypovolemia, especially when colloid fluids are used.[30]

Preexisting losses that are entirely water come from all body compartments, with two thirds of the lost volume being taken from the intracellular space and one third from the extracellular compartment. The patient is hypernatremic. These patients are dehydrated in the strict sense of the word; they have suffered a water loss. Shock fluids should have a sodium concentration equal to the patient's current sodium concentration until signs of shock are resolved, in order to avoid sudden changes in serum sodium concentration that can have life-threatening consequences.

To create a shock resuscitation fluid for a hypernatremic patient, an appropriate amount of hypertonic saline is added to a bag of 0.9% saline. Hypertonic saline at a concentration of 23.4% (Na = 4 mEq/ml) is useful for this purpose. The aim is to make a fluid with a sodium concentration close (within 5 mEq/L) to the patient's serum sodium concentration. There is some variation in sodium concentration and in the actual volume (slightly overfilled) in bags of fluid. One can analyze the baseline sodium concentration of the fluid and weigh the bag before calculating the volume of hypertonic saline to add. The resultant fluid can be given safely as a bolus in large amounts, if needed, to the hypernatremic patient. Once the patient has been resuscitated, a fluid therapy plan to resolve the hypernatremia is indicated (see Chapter 54, Sodium Disorders).

65.7.2 Preexisting Volume Excess

Extracellular volume excess (edema) may occur from administration of isotonic crystalloid fluids in amounts that exceed the patient's output capacity. These patients have peripheral edema and are at risk for pulmonary edema. The vascular-to-interstitial volume ratio in these patients may be as high as 1:6 rather than the normal 1:3. If isotonic crystalloids are administered, they will redistribute out of the vascular space in accordance with the new vascular-to-interstitial volume ratio. Hence shock resuscitation of these patients with isotonic crystalloids is unlikely to provide the desired vascular volume expansion. Hypertonic saline and colloid solutions can be considered, with the caveat that colloid solutions contain isotonic saline.

65.7.3 Active Hemorrhage

In patients with hemorrhage, administration of large volumes of crystalloid or colloid fluids is likely to promote more bleeding. Restraint in the volume prescribed is suggested, but inadequate resuscitation puts the patient at risk for global impairment of tissue perfusion. Control of bleeding before administration of resuscitation (delayed resuscitation) may be feasible if the appropriate facilities and staff are available,[31] but limited early resuscitation to at least minimal end points is likely to be a better option.[32-34]

65.7.4 Brain Injury

Brain-injured patients suffering from shock must be resus-citated adequately. Outcomes have been shown to be poorer for human patients with brain injury when they are not fully resuscitated to end points such as restoration of adequ-ate blood pressure.[35] If otherwise indicated, hypertonic saline combined with a colloid is a good choice (see Chapters 100 and 152, Intracranial Hypertension and Traumatic Brain Injury, respectively).

65.8 CRYSTALLOIDS OR COLLOIDS

The increase in blood volume expected at the end of rapid infusion is different among isotonic or hypertonic crystalloids or colloids. In experimental healthy dogs given the usual doses at rapid rates, the end-infusion blood volume was about 76% for isotonic saline (80 ml/kg in 12 minutes), 25% for colloids (20 ml/kg in 5 minutes), and 17% for hypertonic saline (4 ml/kg in 5 minutes). At 30 minutes post infusion the blood volume for isotonic crystalloids or colloids was approximately equal at 35%, and was 12% for hypertonic saline. What is not established is whether the initial, larger increase in blood volume obtained with isotonic crystalloids is better than the more modest increase gained with colloids. Hypertonic saline should usually be combined with another fluid to ensure more vascular volume expansion. The volume expansion achieved at the end of rapid infusion is dependent on the volume administered, and that obtained after 30 minutes is dependent on the characteristics of the fluid.

Many randomized, controlled clinical trials of crystalloids compared with colloids for treatment of shock in human patients have been performed and several metaanalyses of these trials published.[36-38] Overall, there were no consistent differences in outcome. However, subgroup analysis showed that the use of isotonic crystalloids in trauma patients was associated with improved survival. A recent review concluded that there was no evidence that resuscitation with colloids reduced the risk of death.[39]

A clinical trial in dogs suffering from trauma compared a hypertonic saline and dextran combination with isotonic crystalloids for resuscitation and found no significant differences in the responses measured.[40] Considering these and other clinical trials, and especially considering the differences among patients, it is likely that equivalent effects can be expected when any of these fluids is used appropriately and titrated to the same end points.

65.8.1 Venous Access and Fluid Delivery Systems

Fluids for shock are delivered intravenously or by the intraosseous route. Other routes, such as subcutaneous and intraperitoneal, are not desirable, because shock-induced vasoconstriction impairs absorption by these routes. The fluid delivery system should be chosen so that a large volume can be delivered at a fast rate. The best choice is usually a large-gauge, short catheter with a short length of tubing between the fluid and the patient. The flow rate can be raised by adding a pressure bag to the delivery system.

65.8.2 End Points of Resuscitation

Fluid therapy for shock is continued until end points have been reached. The most common end points are improvements in mental state, mucous membrane color, capillary refill time, pulse rate, and pulse quality. Improvements in hyperlactatemia or base deficit are expected, if these were abnormal before treatment. Other end points of resuscitation, such as mixed venous oxygen saturation and oxygen extraction ratio, have also been used. Early goal-directed therapy where end points of resuscitation such as oxygen content and central venous hemoglobin saturation were maximized early was found to be beneficial in human patients in septic shock and is recommended.[41]

65.8.3 Fluid Challenge

One of the limits of the physical examination is the evaluation of vascular volume status. This is a significant limit, because vascular volume is an important contributor to delivery of oxygen and other nutrients to metabolically active cells, which is the goal of fluid therapy for shock. A practice that is complementary to physical evaluation of vascular volume status is to use response to therapy, also called *fluid challenge,* which has been reviewed.[42] The fluid challenge technique is for hemodynamically unstable patients. The goal is to optimize cardiac filling pressures and forward blood flow. If the parameters of concern (restoration of arterial blood pressure, improvement of physical parameters related to tissue perfusion, and improved diuresis) improve after the fluid challenge, then there was a vascular volume deficit even if the physical examination did not clearly identify it. Also, failure to respond to a fluid challenge raises the question of whether the patient has a cause of shock other than vascular volume deficit. In such patients more advanced hemodynamic monitoring may be indicated (see Chapters 203 and 212, Hemodynamic Monitoring and Cardiac Output Monitoring, respectively). The fluid challenge technique is useful in patients whose physical examination is equivocal.

For a fluid challenge to be effective it must be of sufficient volume and be given rapidly enough that a change in cardiovascular status can be appreciated. Suggested dosages are 10 to 20 ml/kg of an isotonic crystalloid fluid (for cats and dogs, respectively) or 3 to 5 ml/kg of a colloid fluid (for cats and dogs, respectively) infused over 10 minutes (see Table 65-1).

65.9 SUGGESTED FURTHER READING*

TK Day, S Bateman: Shock syndromes. In SP DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders*. ed 3, 2006, Saunders, St Louis, *An excellent reference text for all aspects of fluid therapy*.

B Driessen, B Brainard: Fluid therapy for the traumatized patient. *J Vet Emerg Crit Care*. **16**, 2006, 276, *A comprehensive veterinary review paper*.

ER Schertel, DA Allen, WW Muir, et al.: Evaluation of a hypertonic saline-dextran solution for treatment of dogs with shock induced by gastric dilatation-volvulus. *J Am Vet Med Assoc*. **210**, 1997, 226, *Hypertonic saline and dextrans compared with lactated Ringer's solution, both effective*.

DC Silverstein, J Aldrich, SC Haskins, et al.: Assessment of changes in blood volume in response to resuscitative fluid administration in dogs. *J Vet Emerg Crit Care*. **15**, 2005, 185, *Experimental study of continuous measurement of hematocrit during and after administration of resuscitation fluids demonstrating the minute-to-minute various effects of isotonic crystalloid, colloid, or hypertonic saline on blood volume*.

B Vallet, E Wiel, G Lebuffe: Resuscitation from circulatory shock. In MP Fink, E Abraham, JL Vincent, PM Kochanek (Eds.): *Textbook of critical care*. ed 5, 2005, Saunders, Philadelphia, *One of the definitive textbooks in human medicine for the care of critically ill patients. Most sections, especially those on common problems, and basic science applicable to veterinary patients*.

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* See the CD-ROM for a complete list of references

66 Chapter 66 Transfusion Medicine

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66.1 KEY POINTS

- Transfusion therapy refers to the safe and effective replacement of blood or one of its components, thereby offering support for many critically ill anemic or bleeding patients.
- The indications for transfusions need to be clearly determined, and ideally only the deficient blood component is replaced at the appropriate dosage.
- Although red blood cells and plasma clotting factors are crucial, the indications and efficacy of transfusing platelets, leukocytes, and other plasma proteins are limited.
- Blood products represent a limited resource; hence they should be given only when indicated, using the minimal dosage required and after carefully considering all alternatives.
- All canine and feline donor blood must be typed for the dog erythrocyte antigen (DEA) 1.1 and the feline AB blood groups, respectively, and all donors must have regular health examinations including blood and infectious disease screening.
- All canine and feline recipient blood should be typed for DEA 1.1 and feline AB blood groups, respectively. Blood from any previously transfused (more than 4 days prior) animal should also be crossmatched before receiving another red blood cell transfusion.
- Although acute hemolytic transfusion reactions are feared most, they can be avoided by prior compatibility testing; other transfusion reactions may not be predictable.
- The efficacy and survival of transfused blood cells and plasma proteins should be monitored during and after transfusion using appropriate clinical and laboratory parameters.

66.2 INTRODUCTION

Since the early 1980s, blood product administration to treat critically ill animals or those undergoing surgical procedures has increased tremendously. However, it is important to note that blood products are obtained from donor animals and represent a limited resource that is not available in all situations. Because they are biologic products, they bear the inherent risks of transmitting infectious diseases or causing other adverse reactions. Clinicians in the critical care setting play a key role in providing safe and effective transfusion therapy and therefore should be aware of the principles of transfusion medicine. The interested reader is referred at the end of the chapter to more comprehensive reviews and books on veterinary transfusion medicine.

66.3 INDICATIONS FOR TRANSFUSION THERAPY

Blood transfusions are indicated for management of anemia, coagulopathy, and rarely for other conditions such as thrombocytopenia, thrombopathia, and hypoproteinemia (Table 66-1). The disorders that lead to these medical problems and their detailed management are described in separate chapters. Fresh whole blood (FWB) contains all cellular and plasma components of blood, but specific blood component therapy provides the most effective and safest support and allows for optimal use of every donation. The decision to transfuse is based on the overall clinical assessment of a patient's history and clinical signs, routine laboratory test results, underlying cause, and sound clinical judgment. Although the optimal packed cell volume (PCV) may be above 30%, oxygen delivery in a normovolemic resting animal can be maintained down to a Hct of 10% (although this is inadequate under most disease conditions). Thus there is no specific transfusion trigger in all patients (i.e., certain PCV or coagulation times). Because transfusion carries inherent risks, blood should never be given without a clear indication or before exhausting alternative therapies. Furthermore, blood components represent a scarce resource and should therefore not be used without a proper indication and assessment of the prognosis.

66.3.1 Red Blood Cell Transfusions

The most common indication for transfusions in dogs and cats is anemia (see Chapter 120, Anemia). Transfusions are generally required after loss of the blood's oxygen-carrying capacity (i.e., loss of hemoglobin) and subsequent tissue/organ ischemia, and not as a simple volume expander. Depending on the type, degree, rapidity, and course of the anemia, a transfusion with blood products, such as stored packed red blood cells (pRBCs), fresh whole blood FWB, or stored whole blood, may be warranted. Animals with rapidly progressive anemia should be transfused when the Hct is approximately 20% to 25%, and a patient with chronic anemia may not require transfusion despite having a much lower Hct.

Healthy animals can readily tolerate a loss of up to 20% of blood volume (blood donors regularly give 20 ml/kg body weight q6-12wk) without any ill effects. However, animals with acute hemorrhage exceeding 20% of the blood volume may require a blood transfusion in addition to the initial shock fluid therapy (see Chapter 65, Shock Fluids and Fluid Challenge). It should be noted that animals with peracute blood loss will not show a drop in Hct for hours following hemorrhage, until intercompartmental fluid shifts occur or fluid therapy is instituted. Hence, other parameters are used to decide if transfusion therapy is indicated, such as mucous membrane color, capillary refill time, heart rate, blood pre-ssure, and possibly blood lactate levels. An assessment of an arterial blood gas and respiratory rate and effort are useful to evaluate animals with coexisting respiratory disease (ventilation-perfusion mismatch). In most animals with anemia secondary to acute blood loss, fluid therapy alone 281 will restore 282 vital organ perfusion, although pRBCs should be considered in any animal with evidence of tissue hypoxia. A falling Hct is not a contraindication of fluid administration, although excessive blood collection for diagnostic tests may necessitate blood replacement in a sick animal. Animals that require anesthesia and surgery should have a Hct of at least 20% to ensure adequate oxygen-carrying capacity during anesthesia.

Table 66-1 Blood Products, Storage Guidelines, and Indications

Blood Product	Storage	Temperature in Celsius	Indications
Fresh whole blood (FWB)	<8 hours	2 to 24	Combined red blood cell and plasma deficiency with need for platelets
FWB	<24 hours	4	Combined red blood cell and plasma deficiency without need for platelets
Stored whole blood (SWB)	28 to 35 days	4	Anemia Hypoproteinemia
pRBC	28 to 35 days	4	Anemia
Platelet rich plasma (PRP) or platelet concentrates	24 hours*	20-24	Thrombocytopenia with life-threatening bleeding
Fresh frozen plasma (FFP)	1 year	<−20 to −40	Any coagulation factor deficiencies; hypoproteinemia
Stored plasma	1 to 2 years	<−20 to −40	Hypoproteinemia
Cryoprecipitate (CRYO)	1 year	<−20 to −40	von Willebrand disease Hemophilia A (but not B) Hypofibrinogenemia
Cryoprecipitate-poor plasma (CRYO-poor)	1 year	<−20 to −40	Hypoproteinemia Some coagulopathies (factors II, VII, IX, XI)

In animals with immune-mediated hemolytic anemia (see Chapter 121, Acute Hemolytic Disorders), red blood cell transfusions have proven lifesaving and there is no evidence that transfused red blood cells are destroyed more rapidly than the patient's own erythrocytes. There are no data to show that the transfused cells “add fuel to the fire.” The administration of a bovine hemoglobin solution (Oxyglobin) has also shown beneficial effects.

* If constantly mixed gently.

66.3.2 Fresh Frozen Plasma

Fresh frozen plasma (FFP) is used most commonly in veterinary practice to treat coagulopathies causing serious bleeding, because this product contains all coagulation factors. FFP is commonly used in animals with hemorrhage secondary to acquired coagulopathies (i.e., liver disease and anticoagulant rodenticide intoxications) or patients with hereditary coagulopathies and subsequent bleeding. Sudden hemorrhage caused by therapeutically used heparin (including accidental use of undiluted heparin flushes) or warfarin to counter thrombosis can also be corrected with FFP, although protamine can also reverse the heparin-induced effects. The use of FFP (with or without heparin) to replace deficient coagulation factors and antithrombin to treat patients with immune-mediated hemolytic anemia or disseminated intravascular coagulation is controversial. There are no studies documenting a definitive beneficial effect. Similarly, evidence for the use of FFP in animals with acute pancreatitis (to replace α-macroglobulins and antiproteases) or in parvovirosis (to provide antiparvovirus antibodies and additional immunoglobulins and to stop gastrointestinal hemorrhage) is lacking. FFP is also commonly used to correct hypoproteinemias in cases of protein-losing nephropathies and enteropathies, but its effect on oncotic pressure in these animals is minimal at clinically used dosages, especially when compared with synthetic hyperoncotic agents such as dextran-70 or hydroxyethyl starch. Critically ill animals with albumin concentrations less than 1.5 g/dl may benefit from plasma therapy, because this protein is an important carrier of certain drugs, hormones, metals, chemicals, toxins, and enzymes.

66.3.3 Other Blood Products

Other blood products are used less commonly in dogs and are not generally available for cats. Cryoprecipitate is rich in fibrinogen, fibronectin, factor VIII, and von Willebrand factor and is the preferred treatment for bleeding dogs with these plasma protein deficiencies. If available, cryoprecipitate-poor plasma may be administered to many coagulopathic and hypoproteinemic dogs when synthetic plasma expanders are of limited use or have undesirable side effects. Because platelets are relatively short-lived (1 week) and cannot readily be stored for any length of time (<24 hours at room temperature), they rarely are transfused. Hemorrhage caused by thrombocytopenia in anemic dogs could be treated with FWB, but generally requires only pRBCs to correct the anemia. Rarely, platelet-rich plasma (PRP) and platelet concentrates are required to control life-threatening bleeding (see Chapter 119, Thrombocytopenia). Furthermore, in dogs with immune-mediated thrombocytopenia, transfused platelets have a very short half-life (hours) and will not result in any appreciable platelet rise, but they may transiently stop severe hemorrhage. Althouh cryopreserved platelets are currently available for use in dogs, there is insufficient information to document their efficacy or to recommend routine use of the product. Research is ongoing. Because of the very short half-life of granulocytes (hours), leukocyte transfusions are not generally practiced in human or veterinary medicine.[1]

66.4 BLOOD TYPING

To ensure efficacious and safe transfusions, blood from both donor and recipient should be typed and, if previously 282
283 transfused, a crossmatch should also be performed. Blood types are genetic markers on erythrocyte surfaces that are species-specific and antigenic in individuals that lack the same markers. This antigenicity results in the development of alloantibodies, so that the administration of a small volume (as little as 1 ml) of incompatible blood can result in life-threatening reactions. Blood typing is therefore clinically important to ensure blood compatibility and is recommended for any animal in need of a transfusion, any animal becoming a blood donor, and before breeding type B queens to avoid neonatal isoerythrolysis (NI). Unless blood typing is performed regularly, it is best to send ethylenediaminetetraacetic acid (EDTA) blood to a laboratory for typing.[2,3]

66.4.1 Canine Blood Types

Dogs have more than a dozen blood group systems known as DEAs. Canine erythrocytes are either positive or negative for a blood type (e.g., DEA 4 positive or negative), and these blood types are thought to be codominantly inherited. In the DEA 1 system, which represents an exception, DEA 1.1 (A_1) and 1.2 (A_2) are allelic, and there may even be a DEA 1.3 (A_3). Thus a dog can be DEA 1.1 positive or DEA 1.1 negative, and only DEA 1.1-negative dogs can be DEA 1.2 positive or DEA 1.2 negative. There are no clinically important alloantibodies present before sensitization of a dog with a transfusion (pregnancy has never been reported to cause sensitization).[2,4,5]

The most important canine blood type is DEA 1.1. DEA 1.1 (A_1) elicits a strong alloantibody response after sensitization of a DEA 1.1-negative dog by a DEA 1.1-positive transfusion. This can lead to an acute hemolytic transfusion reaction in a DEA 1.1-negative dog previously transfused with DEA 1.1-positive blood. Transfusion reactions against other blood types in previously transfused dogs have been described rarely. They include reactions against the DEA 4,[6] Dal in Dalmatians, and another common red blood cell antigen in a Whippet. Additional clinically important blood types may yet be discovered.[7]

Simple blood typing cards using a DEA 1.1 monoclonal antibody are available for DEA 1.1 typing of dogs (DMS Laboratories, Flemington, NJ), but there is some concern that weak agglutination reactions may be caused by the DEA 1.2 antigen. More recently, a reliable gel column procedure has been introduced (DiaMed, Cressier, Switzerland) for clinical pathology laboratories. Ethylenediaminetetraacetic acid is preferred over other anticoagulants.[8] Dogs that are DEA 1.1 negative are considered universal blood donors for a dog that has never been transfused. Canine blood typing sera for DEA 1.1, 1.2, 3, 4, and 7 and limited typing services are available (Midwest Blood Services, East Lansing, MI), but other blood groups of clinical importance can be identified by crossmatching previously transfused dogs. Persistent autoagglutination following saline washing of the recipient's blood negates any typing and crossmatch testing. Unless a bitch has been transfused previously, there is no concern for NI.

66.4.2 Feline Blood Types

The main blood group system recognized in cats is known as the *AB blood group system* and consists of three types: type A, type B, and the extremely rare type AB. Type A is dominant over B.[9-11] Thus cats with type A blood have the genotype a/a or a/b, and only homozygous b/b cats express the type B antigen on their erythrocytes. In the extremely rare AB cat, a third allele recessive to a or codominant to b (or both) leads to the expression of both A and B substances. Cats with type AB blood are not produced by mating of a cat with type A to a cat with type B unless the cat with type A carries the rare AB allele. Cats with type AB blood have been seen in many breeds, including domestic shorthaired cats. The frequency of feline A and B blood types varies geographically and among breeds. For instance, all Siamese cats have type A blood, and Turkish Vans and Angoras have equal numbers of type A and B blood. Most domestic shorthaired cats have type A blood, but the proportion of cats with type B blood can be substantially different in certain geographic areas. All donor blood must be typed. Most blood donors have type A blood, but some clinics also keep cats with the rare type B and type AB blood as donors.[2]

Cats have naturally occurring alloantibodies.[9] All cats with type B have very strong naturally occurring anti-A alloantibodies. Kittens receive alloantibodies through the colostrum from type B queens and develop high alloantibody titers (>1:32) after a few weeks. Anti-A alloantibodies are responsible for serious transfusion reactions and NI in kittens with type A and AB born to type B queens. Cats with type A blood have weak anti-B alloantibodies, and their alloantibody titer is usually very low (1:2). Nevertheless cats with type A blood can also develop hemolytic transfusion reactions when given B blood, but no type A queen has had a litter with NI caused by AB incompatibility. Cats with type AB blood have no alloantibodies, although it is recommended that these cats receive type A pRBCs if type AB blood is not available. Furthermore, additional blood group systems are being identified, such as the Mik red blood cell antigen in domestic shorthaired cats. It is thought that Mik-negative cats may produce naturally occurring alloantibodies, leading to blood incompatibility reactions beyond the AB blood group system.[12]

Simple AB blood typing cards are available for use in practice (DMS Laboratories, Flemington, New Jersey), but there are occasionally concerns that cats with type AB are not being recognized. More recently, a gel test (DiaMed, Cressier, Switzerland) has been introduced as an accurate laboratory method, in addition to the regular tube and slide tests used in laboratories.[13]

66.5 BLOOD CROSSMATCHING

The blood crossmatch detects the serologic compatibility between the anemic recipient and potential donor, and must be performed in cats if blood typing is not available and in dogs or cats that have previously received transfusion therapy.[1,2,10] This test looks for the presence or absence of alloantibodies in dogs or cats without determining the blood type; it does not replace blood typing. Crossmatching is done with anticoagulated blood from the recipient and the potential donor and requires some technical expertise, but may be performed in practice along with blood typing. Gel-based techniques for standardized crossmatching are being introduced. The major crossmatch tests for alloantibodies in the recipient's plasma against donor cells. The minor crossmatch tests for alloantibodies in the donor's plasma against recipient's red blood cells and is of lesser importance, because the donor's plasma will be diluted. It is also of lesser importance if all donors' types are known and if the donors have never received transfusions (i.e., no prior sensitization). Autoagglutination or severe hemoglobinemia (secondary to fragile red blood cells) precludes testing. Washing the red blood cells three times with physiologic saline may prevent autoagglutination and rouleaux formation.

Because dogs do not have naturally occurring alloantibodies, the initial crossmatch of a dog that has not previously been transfused should be compatible.[4] A compatible crossmatch in a dog does not prevent sensitization against donor cells within 1 to 2 weeks. Thus a dog that was previously given a compatible transfusion from a donor dog may become incompatible with blood from the same donor 1 to 2 weeks later. Because cats have naturally occurring alloantibodies, a blood crossmatch test can detect an A-B mismatch as well as other incompatibilities (e.g., Mik). Mixing a drop of donor blood with recipient plasma (or vice versa) will detect the strong A-B incompatibilities. The practice of administering a small amount of blood to the recipient animal to test for compatibility should be abandoned, because it may result in fatal transfusion reactions.

66.6 BLOOD DONORS AND SOURCES

Many larger veterinary hospitals have permanent canine and feline blood donors to cover their transfusion requirements or in case FWB or PRP (platelet concentrates) is needed. Several larger voluntary blood donor programs have emerged with client-owned or staff-owned dogs. More than a dozen commercial canine blood banks have been established in the United States that deliver blood products overnight; however, there is generally a blood shortage. Some blood banks are also providing feline products. Autologous (self) transfusion refers to the donation of blood by a patient from 4 weeks to a few days before a surgical procedure during which large surgical blood loss is anticipated. Blood can also be collected immediately before surgery. The patient's blood is diluted with crystalloid and colloid solutions, and the previously drawn blood is replaced when excessive bleeding occurs during or after surgery. Autotransfusion is another autologous transfusion technique in which shed blood salvaged intraoperatively or following intracavitary hemorrhage is reinfused after careful filtering. However, blood from longstanding (more than 1 hour), contaminated, or malignant hemorrhagic effusions should not be reinfused.

Blood donors should be young adult, lean, and good-tempered animals and weigh at least 25 kg for dogs to donate 450 ml or 4 kg for cats to donate 40 ml. They should have no history of transfusion and be regularly vaccinated and healthy as determined by history, physical examination, and laboratory tests (complete blood cell count, chemistry screen and fecal parasite examination every 6 to 12 months), as well as free of infectious diseases. Testing depends on species, breed, and geographic area but may include regular microfilaria, *Brucella, Babesia, Ehrlichia, Anaplasma, Borrelia,* and *Leishmania* spp testing in dogs and feline leukemia virus, feline immunodeficiency virus, feline infectious peritonitis, and *Mycoplasma haemofelis* (previously named *Haemobartonella felis*) testing in cats. Donors should receive a well-balanced, high-performance diet, and may be supplemented twice weekly with oral ferrous sulfate (Feosol, 10 mg/kg q24h) if bled every 4 weeks. PCV or hemoglobin concentration should be over 40% and more than 13 g/dl, respectively, in canine donors and over 30% and more than 10 g/dl, respectively, in cats.[14]

66.7 BLOOD COLLECTION

Canine donors generally are not sedated, but cats regularly require sedation. Some sedatives, such as acepromazine, interfere with platelet function and induce hypotension and therefore should not be used. Blood is collected aseptically by gravity flow or blood bank vacuum pump from the jugular vein over a 5- to 10-minute period. Plastic blood bags (Fenwal) containing citrate-phosphate-dextrose-adenine (CPD-A_1), with or without satellite bags for blood component separation, are optimal. These commercial blood bags represent a closed collection system in which the blood does not come into contact with the environment at any time during collection or separation into blood components, thus minimizing the risk of bacterial contamination and allowing for rapid storage of the blood products. Large plastic syringes containing 1 ml CPD-A_1 or 3.8% citrate per 9 ml blood and connected to a 19-gauge butterfly needle are used commonly for blood collection in cats. This represents an open collection system in which connections allow exposure of blood to the environment.[15] Because of the risk of bacterial contamination, blood collected via an open system should not be stored for more than 48 hours. Vacuum glass bottles containing acid-citrate-dextrose allow rapid collection, but are not recommended because blood components are damaged readily and cannot be separated and stored for long periods. The maximal blood volume to be donated is 20 ml blood/kg or one regular blood bag unit of 450 ± 50 ml per ≥25-kg dog and 10 ml blood/kg or 40 ml blood (one typical feline unit) per ≥4-kg cat.

Blood components are prepared from a single donation of blood by simple physical separation methods such as centrifugation within 8 hours of collection; thereby, FWB can be separated into pRBCs, PRP or platelet concentrates, FFP, cryoprecipitate, and cryoprecipitate-poor plasma according to the *Technical Manual of the American Association of Blood Banking,* but this does require some expertise and equipment. Blood component preparation is best accomplished by using plastic blood bags with satellite transfer containers to ensure sterility. Fluctuations in storage temperature significantly alter the length of storage; thus, FWB and pRBCs should be kept at 4° C ± 2° C and all plasma products at less than −20°C using blood bank refrigerators and freezers with alarms, if possible. Alternative refrigerator-freezer devices may be used as long as the temperature is monitored and the unit is not opened frequently. Storage of canine pRBCs will result in a gradual reduction of erythrocytic 2,3-diphosphoglyceride and accumulation of ammonia, but these metabolites are rapidly regenerated or eliminated, respectively, and do not typically affect pRBC efficacy or safety. Caution must be exercised, however, in animals that have severe liver insufficiency and subsequent hyperammonia. Blood components that have been warmed to room or body temperature should not be recooled or stored again because of safety (affects product quality). Similarly, partially used or opened blood bags should be used within 24 hours because of the risk of contamination and product damage.

66.8 ADMINISTRATION OF BLOOD PRODUCTS

For routine transfusion therapy in anemic patients, it is not necessary to warm blood after removal from the refrigerator. Warming may accelerate the deterioration of stored red blood cells and permit rapid growth of contaminating microorganisms. However, there are specific clinical situations (such as transfusion of neonates or resuscitation of trauma patients) that necessitate the administration of rapid, massive transfusions such that warming of the blood products is indicated to prevent complications associated with hypothermia (e.g., cardiac arrhythmias and coagulopathies). A temperature-controlled waterbath or bowl (39° C or 102.2° F) is used to warm the blood products. Care should be taken to maintain absolute sterility and not to overheat any part of the blood products to over 39° C.

Blood bags are connected to infusion sets that have an in-line microfilter. A long (85 cm) blood infusion set with a drip chamber for medium to large dogs and a short infusion set that can be attached to a syringe for small dogs and cats are available. A latex-free infusion set should be used for platelet administration to prevent aggregation. Microfilters with 170-μm pores are used commonly to remove clots and larger red blood cell and platelet aggregates. Finer filters with 40-μm pores will remove most platelets and microaggregates, but these commonly clog or become dysfunctional after 50 to 100 ml of blood is run through them. Leukocyte reduction filters may be used at the time of blood collection to decrease febrile adverse reactions to white blood cell components, but they are expensive. Sterility must be maintained when connecting the blood component bag to the infusion set and the tubing to the catheter.

Blood components are best administered intravenously. An intramedullary (intraosseous) catheter may be used when venous access cannot be obtained (see Chapter 62, Intraosseous Catheterization). Intraperitoneal administration is not generally recommended because absorption time is delayed. Concurrent administration of drugs or fluids other than physiologic saline should be avoided to prevent lysis of erythrocytes or coagulation. Thus fluids containing calcium or glucose, or hypotonic or hypertonic solutions should not be administered simultaneously through the same intravenous line.

The rate of transfusion depends on the cardiovascular status, hydration status, degree of anemia, and general condition of the recipient. The initial rate should be slow, starting with 1 to 3 ml over the first 5 minutes, to observe for any transfusion reactions, even with blood-typed or crossmatched transfusions. In animals with cardiac failure, 4 ml/kg/hr should be used for administration, and close monitoring is of utmost importance. Transfusion of a single bag should be completed within 4 hours to prevent functional loss or bacterial growth. The volume of the blood component to be administered depends on the type of deficiency and size of the animal. For treatment of anemia:

> Volume (ml) of whole blood = 2 × PCV rise desired (%) × body weight (kg). In other words, administration of 2 ml whole blood/kg body weight raises the PCV by 1%. If pRBCs are used without prior resuspension in a red blood cell preservative, half the volume should be administered, because pRBCs have a PCV of 70% to 80%.

In the absence of bleeding and hemolysis, at least 70% of transfused erythrocytes survive 24 hours (required blood bank standard) and transfused erythrocytes may thereafter be expected to have a near normal life span (approximately 70 days in cats, 110 days in dogs). The response to the transfusion is monitored by obtaining a PCV and total protein reading before, during, and 6 and 24 hours after transfusion, and the clinician must consider continued blood loss and hemolysis when interpreting values.

In animals with thrombocytopenia or thrombopathia, one unit of platelet concentrates, PRP, or FWB will increase the platelet count by approximately 10,000/μL in a recipient weighing 30 kg. In animals with serious or life-threatening bleeding, the platelet count should be increased to greater than 20,000 to 50,000/μl. Platelet counts should be monitored before and 1 and 24 hours after platelet transfusion.

> In bleeding animals with coagulopathies and von Willebrand disease, FFP is initially administered at a dosage of 6 to 10 ml/kg to stop bleeding or prevent excessive bleeding during surgery.

In some cases, larger volumes may be needed to control bleeding, and depending on the coagulopathy, repeated administration of FFP may be required. Because of the short half-life of factors VII, VIII, and von Willebrand factor, deficient animals may need treatment 2 to 4 times daily. Animals with other coagulopathies may be treated daily. Plasma support should be provided for an additional 1 to 3 days after the bleeding has been controlled to prevent rebleeding and enhance healing.

> Cryoprecipitate at a dosage of 1 CRYO unit/10 kg or 1 to 2 ml/kg body weight twice daily is ideal to treat a bleeding animal with hemophilia A and/or von Willebrand disease.

66.9 ADVERSE TRANSFUSION REACTIONS

Although transfusion of blood and its components is usually a safe and temporarily effective form of therapy, there is always some risk involved. Adverse reactions usually occur during or shortly after the transfusion and can be caused by any component of the infused blood product. Most transfusion reactions can be avoided by carefully selecting only healthy donors, using appropriate collection, storage, and administration techniques, performing blood-typing and crossmatching, and administering only necessary blood components. The most common clinical sign of a transfusion reaction is fever, followed by vomiting and hemolysis; any reaction should lead to immediate cessation of the transfusion. Hemolytic transfusion reactions can be fatal and are therefore most important, but fever and vomiting are usually self-limiting. Adverse effects of transfusions can be divided into nonimmunologic reactions (pyrogen-mediated fever, transmission of infectious agents, vomiting, mechanical hemolysis, congestive heart failure, hypothermia, citrate toxicity, and pulmonary complications) and immunologic reactions (acute and delayed hemolytic transfusion reactions, manifestations ranging from urticaria to anaphylaxis, and graft versus host disease). Note that some clinical signs may be caused by both mechanisms.

Diphenhydramine (2 to 4 mg/kg IM, SC, or IV once) and glucocorticoids (antiinflammatory dose equivalents) may be given therapeutically and the transfusion may be continued, if necessary, as long as a hemolytic reaction or 285
bacterial contamination has been excluded and the clinical signs are minimal. Prophylactic use of these medications 286
has not been documented, but withholding food and any other medications during the transfusion does prevent some reactions. Anaphylaxis occurs very rarely and is treated like any other serious allergic reaction (i.e., epinephrine). There is no specific therapy for hemolytic transfusion reactions, but supportive care is indicated. Fortunately, companion animals are resistant to heme protein–induced renal shutdown (also known as pigment nephropathy).

66.10 ALTERNATIVES

Because blood is a scarce resource and may cause significant transfusion reactions, alternatives should be considered. In many animals, treatment of the underlying disease and other supportive measures are all that is needed. Crystalloid and colloid fluids are appropriate when hypovolemia and low oncotic pressure are the main concerns. In the case of tissue hypoxia due to a lack of red blood cells (hemoglobin), bovine ultrapurified hemoglobin solution (Oxyglobin) can be used as a blood substitute in place of pRBCs, although its future availability is questionable. Oxyglobin is approved for dogs and has been effective and safe as a transient oxygen carrier in various clinical case series in cats. Because of its strong oncotic properties, hypervolemia and pulmonary edema are of particular concern in cats and otherwise compromised patients when large volumes are administered. Furthermore, the potential benefit of perfusing the capillary beds with oxygen transported by free hemoglobin rather than red blood cells may be countered by some of the adverse cardiovascular effects of Oxyglobin. Placing a critically ill animal in an oxygen cage with an inspired oxygen concentration greater than 21% adds little to the oxygen delivery in an anemic patient (due to a lack of hemoglobin), but it does allow the animal to rest away from the hustle of a busy treatment room and will increase the oxygen content slightly. Furthermore, anemic animals with concomitant pulmonary disease (as often occurs with immune-mediated hemolytic anemia due to pulmonary thromboemboli or pneumonia) will benefit from oxygen supplementation. Although human recombinant erythropoietin has a role in the treatment of anemia due to chronic renal failure and a few other types of anemia, its effect is delayed and it is thus not effective for the critical care patient and does carry the risk of causing crossreacting anti-erythropoietin antibodies.

Although various recombinant human products are available as alternatives for supplementation of plasma proteins in human medicine, these treatment options have not been evaluated completely in small animals and may not be safe or cost effective. Human albumin concentrates have been used in dogs and cats with severe hypoalbuminemia, but serious concerns have arisen regarding its safety and efficacy (lack of impact on survival in humans). Recombinant coagulation factors have drastically reduced the use of FFP in human patients. For instance, recombinant human FVIIa has been evaluated in dogs with factor VII deficiency and other hemostatic diatheses. Similarly, there is no commercial product of a canine or feline immunoglobulin concentrate, and thus human intravenous immunoglobulin has been used successfully in the acute treatment of dermal and systemic toxic drug reactions, as well as the treatment of severe immune-mediated diseases. Again, these are human products that bear the risk of reactions, especially with repeated use. In conclusion, a good understanding of transfusion medicine and its benefits and risks is crucial for today's emergency clinician.

66.11 SUGGESTED FURTHER READING*

M Brecher: In *AABB technical manual*. ed 15, 2006, American Association of Blood Banks, Baltimore, MD, *Detailed description of human blood banking procedures that represents general standards for veterinary transfusion medicine*.

SM, Cotter (Ed.): In *Comparative transfusion medicine*. 1991, Academic Press, San Diego, *A comprehensive review of veterinary transfusion issues*.

U Giger: Blood typing and cross-matching to ensure compatible transfusions. In JD Bonagura (Ed.): *Kirk's current veterinary therapy XIII*. 2000, Saunders, Philadelphia, *A review of the blood type compatibility issues for transfusion medicine*.

ME Griot-Wenk, U Giger: Feline transfusion medicine: Feline blood types and their clinical importance. *Vet Clin North Am Small Anim Pract*. **25**, 1995, 1305, *A review of practical feline transfusion medicine*.

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* See the CD-ROM for a complete list of references

67 Chapter 67 Diabetic Ketoacidosis

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67.1 KEY POINTS

- Diabetic ketoacidosis (DKA) is a severe form of complicated diabetes mellitus that requires emergency care.
- Acidosis and electrolyte abnormalities can be life threatening.
- Fluid therapy and correction of electrolyte abnormalities are the two most important components of therapy.
- Concurrent disease increases the risk for DKA and must be addressed as part of the diagnostic and therapeutic plan.
- Bicarbonate therapy usually is not needed and its use is controversial.
- About 70% of treated dogs and cats are discharged from the hospital after 5 to 6 days of hospitalization.
- The degree of base deficit is associated with outcome in dogs with DKA. Additionally, dogs that have concurrent hyperadrenocorticism are less likely to be discharged from the hospital.

67.2 INTRODUCTION

Diabetic ketoacidosis (DKA) is a severe form of complicated diabetes mellitus that requires emergency care. Ketones are synthesized from fatty acids as a substitute form of energy, because glucose is not transported into the cells. Excess ketoacids result in acidosis and severe electrolyte abnormalities, which can be life threatening.

67.3 PATHOPHYSIOLOGY

Ketone bodies are synthesized as an alternative source of energy when intracellular glucose concentration can not meet metabolic demands. Ketone bodies are synthesized from acetyl-coenzyme A (acetyl-CoA) which is a product of mitochondrial β-oxidation of fatty acids. This adenosine triphosphate (ATP)-dependent catabolism of fatty acids is associated with breakdown of two carbon fragments at a time and results in formation of acetyl-CoA. Synthesis of acetyl-CoA is facilitated by a decreased insulin concentration and increased glucagon concentration. The anabolic effects of insulin include conversion of glucose to glycogen, storage of amino acids as protein, and storage of fatty acids in adipose tissue. Similarly, the catabolic effects of glucagon include glycogenolysis, proteolysis, and lipolysis. Therefore a low insulin concentration and elevated glucagon concentration contribute to decreased mobilization of fatty acids into adipose tissue and increased lipolysis, resulting in elevated acetyl-CoA concentration. In nondiabetics acetyl-CoA and pyruvate enter the citric acid cycle to form ATP. However, in diabetics, glucose does not enter the cells in adequate amounts, and production of pyruvate by glycolysis is decreased. The activity of the citric acid cycle is therefore diminished, resulting in decreased utilization of acetyl-CoA. The net effect of increased production and decreased utilization of acetyl-CoA is an increase in the concentration of acetyl-CoA, which is the precursor of ketone body synthesis.[1]

The three ketone bodies synthesized from acetyl-CoA are β-hydroxybutyrate, acetoacetate, and acetone. Acetyl-CoA is converted to acetoacetate by two metabolic pathways, and acetoacetate is then metabolized to β-hydroxybutyrate or acetone. One of the pathways of acetoacetate synthesis involves condensation of two acetyl-CoA units and the other utilizes three units of acetyl-CoA. Ketone bodies are synthesized in the liver.[1]

Acetoacetate and β-hydroxybutyrate are anions of moderately strong acids. Therefore accumulation of these ketone bodies results in ketotic acidosis. Metabolic acidosis may be worsened by vomiting, dehydration, and renal hypoperfusion.[1] Metabolic acidosis and the electrolyte abnormalities that ensue are important determinants in the outcome of patients with DKA.[2]

One of the beliefs regarding the pathophysiology of DKA had been that individuals that develop DKA have zero or undetectable endogenous insulin. However, in a study that included seven dogs with DKA, five had detectable endogenous serum insulin concentrations, and two of these dogs had endogenous serum insulin concentration within the normal range.[3] Therefore it is possible that other factors, such as an elevated glucagon concentration (or less likely cortisol or catecholamines), contribute to DKA. Glucagon concentration may be elevated as a result of concurrent disease.

67.4 RISK FACTORS

The median age of dogs with DKA is 8 years (range 8 months to 16 years).[2] The mean age of cats with DKA is 9 years (range 2 to 16 years).[4] Breed or sex has not been shown to increase the risk of DKA in dogs or cats.[2,4,5]

Concurrent disease has been documented in about 70% of dogs with DKA and 90% of cats with DKA. The most common concurrent diseases noted in dogs with DKA are acute pancreatitis, bacterial urinary tract infection, and hyperadrenocorticism.[2] The most common concurrent diseases noted in cats with DKA are hepatic lipidosis, chronic renal failure, acute pancreatitis, bacterial or viral infections, and neoplasia.[4] It is possible that concurrent disease results in an elevated glucagon concentration and increased risk of DKA. The role of cortisol and catecholamines remains to be elucidated.

Most dogs and cats with DKA are newly diagnosed diabetics. It is possible that insulin treatment reduces the risk of DKA in dogs and cats.[2,4]

67.5 CLINICAL SIGNS AND PHYSICAL EXAMINATION FINDINGS

Clinical signs and physical examination findings may be attributed to chronic unmanaged diabetes mellitus, concurrent disease, and the acute onset of DKA. The most common clinical signs in dogs or cats with DKA are polyuria and polydipsia, lethargy, inappetence or anorexia, vomiting, and weight loss.[2,4] Common abnormalities noted on physical examination of dogs with DKA are subjectively overweight or underweight body condition, dehydration, cranial organomegaly, abdominal pain, cardiac murmur, mental dullness, dermatologic abnormalities, dyspnea, coughing, abnormal lung sounds, and cataracts.[2] Common abnormalities noted in cats with DKA are subjectively underweight body condition, dehydration, icterus, and hepatomegaly.[4]

67.6 CLINICAL PATHOLOGY

Approximately 50% of dogs with DKA have a nonregenerative anemia (which is not associated with hypophosphatemia), left shift neutrophilia, or thrombocytosis.[2] Anemia and left shift neutrophilia are also common features of feline DKA.[4] These cats also have significantly more red blood cell Heinz body formation than do normal cats, and the degree of Heinz body formation is correlated with plasma β-hydroxybutyrate concentration.[6]

Persistent hyperglycemia is apparent in all dogs and cats diagnosed with DKA, unless they receive insulin.[2] Alkaline phosphatase activity is elevated in almost all dogs with DKA.[2] Alanine aminotransferase activity, aspartate aminotransferase activity, and cholesterol concentration are increased in about half of the dogs with DKA.[2] Elevations in alanine aminotransferase activity and cholesterol concentration are also commonly observed in cats with DKA.[4] Azotemia is reported more commonly in cats than in dogs with DKA.[2,4]

Electrolyte abnormalities are common in both dogs and cats with DKA.[2,4] Initially, an animal with DKA may appear to have extracellular hyperkalemia due to dehydration, decreased renal excretion, hypoinsulinemia, decreased insulin function, hyperglycemia, and acidemia (leading to movement of hydrogen ions into the cells and potassium ions out to maintain cellular electronegativity). However, with rehydration, potassium ions are lost from the extracellular fluid and a true hypokalemia from depletion of total body potassium stores becomes apparent. Hypokalemia may be exacerbated by binding of potassium to ketoacids, vomiting, inappetence, and anorexia, and osmotic diuresis. Insulin therapy may worsen extracellular hypokalemia as insulin shifts potassium into cells.[7] The most important clinical manifestation of hypokalemia in DKA is profound muscle weakness, which may result in respiratory paralysis in extreme cases.

An apparent hypophosphatemia often develops when phosphate shifts from the intracellular space to the extracellular space as a result of hyperglycemia, acidosis, and hypoinsulinemia. Dehydration and decreased phosphorus excretion by the kidneys also contributes to this finding. Osmotic diuresis or fluid therapy along with insulin therapy causes extracellular phosphate depletion, leading to whole body phosphate depletion.[7] Hypophosphatemia related to DKA has been associated with hemolysis (in a cat) and seizures (in a dog).[8] Additional clinical signs that may develop because of hypophosphatemia include weakness, myocardial depression, and arrhythmias.

Decreased plasma ionized magnesium (iMg) concentration has been documented in four of seven cats with DKA, and may be due to increased urinary excretion of magnesium.[9] The clinical significance of hypomagnesemia in cats is unknown. The clinical consequence of hypomagnesemia in humans with diabetes includes insulin resistance, hypertension, hyperlipidemia, and increased platelet aggregation. Dogs with DKA usually do not have low iMg concentrations at the time of initial examination.[2,10] In one study of 78 dogs with uncomplicated diabetes mellitus, 32 dogs with DKA, and 22 control dogs, plasma iMg concentration at the time of initial examination was significantly higher in dogs with DKA than in dogs with uncomplicated diabetes mellitus and control dogs.[10] Hyponatremia, hypochloremia, and decreased ionized calcium concentration have also been documented in about 50% of dogs with DKA. Low sodium concentration may be secondary to the hyperglycemia, leading to a 1 mEq/L decrease in sodium concentration for every 62 mg/dl increase in glucose concentration in humans, and is often referred to as *pseudohyponatremia*. Venous pH is less than 7.35 in all dogs and cats with DKA. Lactate concentration is elevated in about one third of dogs with DKA and is not correlated with degree of acidosis.[2]

Urinalysis is usually indicative of glucosuria. Proteinuria or ketonuria may also be apparent. Ketonuria may not be detected because the nitroprusside reagent in the urine dipstick reacts with acetoacetate and not with β-hydroxybutyrate, which is the dominant ketone body in DKA. Measurement of serum β-hydroxybutyrate is more sensitive than measurement of urine ketones.[11] On urinalysis, the number of white blood cells per high-power field is usually five or fewer, although 20% of dogs with DKA have aerobic bacterial growth on culture of urine obtained by cystocentesis.[2] This is likely a result of immunosuppression of diabetics and decreased ability to mobilize white blood cells to the site of infection.

Results of additional clinicopathologic or imaging tests such as urine culture, abdominal ultrasonography, thoracic radiographs, adrenal or thyroid axis testing, pancreatic lipase immunoreactivity, liver function tests, or liver biopsy depend on concurrent disorders.

67.7 DIFFERENTIAL DIAGNOSIS

Differential diagnoses for ketosis include DKA, acute pancreatitis, starvation, low-carbohydrate diet, persistent hypoglycemia, persistent fever, or pregnancy. Differential diagnoses for a primary metabolic acidosis include DKA, renal failure, lactic acidosis, toxin exposure, severe tissue destruction, severe diarrhea, and chronic vomiting.

67.8 TREATMENT

Administration and careful monitoring of intravenous (IV) fluid therapy is the most important component of treatment (see Chapters 64 and 65, Daily Intravenous Fluid Therapy and Shock Fluids and Fluid Challenge, 289 respectively). Any commercially 290 available isotonic crystalloid solution may be used. The use of 0.9% saline has been advocated because of its relatively high sodium concentration[7]; however, it may be contraindicated in hyperosmolar diabetics. Additionally, 0.9% saline may contribute further to the acidosis because of the high chloride concentration and lack of a buffer. Lactate (contained in lactated Ringer's solution) and acetate (contained in Plasma-Lyte and Normosol-R) are converted to bicarbonate and may contribute to management of acidosis. Another advantage of these buffer-containing crystalloids is that they contain some potassium, which may blunt the acute decline in potassium concentration that the animal could suffer with initiation of fluid and insulin treatment. As long as the patient is monitored carefully, particularly in regard to hydration, mental status, and electrolyte concentrations, any of the above crystalloids can be used for management. Fluid therapy may contribute to a decrease in blood glucose concentration by improving renal perfusion and decreasing the concentration of counter regulatory hormones, most importantly glucagon.[12]

Correction and monitoring of electrolyte abnormalities is the second most important component of therapy. Electrolyte supplementation must be monitored frequently, because frequent adjustments may be required. An animal that appears hyperkalemic at the time of initial examination may become hypokalemic shortly after fluid therapy has begun. Hypokalemia can be treated by administering potassium as an IV constant rate infusion (CRI) at a rate that should generally not exceed 0.5 mEq/kg/hr (Table 67-1). If higher dosages are required, continuous electrocardiographic monitoring should be performed simultaneously.

Hypophosphatemia is corrected with an IV CRI of potassium phosphate (solution contains 4.4 mEq/ml of potassium and 3 mM/ml of phosphate) at a rate of 0.03 to 0.12 mM/kg/hr. Serum potassium concentration must be taken into account when giving potassium phosphate for correction of hypophosphatemia. A magnesium sulfate solution (containing 4 mEq/ml) given intravenously as a CRI of 1 mEq/kg q24h has been used successfully for correction of hypomagnesemia (range 0.5 to 1 mEq/kg q24h). Toxicity from erroneously administered intravenously magnesium has been reported in one diabetic cat and one dog with acute renal disease.[13] Signs of magnesium toxicity in these animals included vomiting, weakness, generalized flaccid muscle tone, mental dullness, bradycardia, respiratory depression, and hypotension.[13] Care must be taken to administer intravenous magnesium only to patients that have documented decreased iMg concentrations. As the hyperglycemia resolves, the sodium concentration is expected to appear higher secondary to the decrease in osmolality and subsequent movement of free water from the intravascular space. If the hyponatremia and hypochloremia persist, they are corrected by administering a 0.9% saline solution.

Table 67-1 Potassium Supplementation in Hypokalemic Animals*

Serum Potassium Concentration (mmol/L)	Potassium (mEq) Added to 250-ml Fluid Bag
1.6–2	20
2.1–2.5	15
2.6–3	10
3.1–3.5	7

Hyperglycemia is corrected with insulin therapy. Although several new rapid-acting products are being used successfully in humans with DKA, their use in dogs and cats has not yet been investigated. Therefore regular insulin is recommended (Humulin R, Novolin R). Regular insulin is administered as an intravenous CRI (Table 67-2)[14] or intramuscularly .[15] When intravenous regular insulin is administered as a CRI, blood glucose is measured every 2 hours. When insulin is administered intramuscularly, it is given every hour, and blood glucose is measured every hour. The initial dose of intramuscular therapy is 0.2 U/kg regular insulin, followed by 0.1 U/kg regular insulin IM 1 hour later. Treatment with IM regular insulin is continued with 0.05 U/kg/hr, 0.1 U/kg/hr, or 0.2 U/kg/hr if blood glucose drops more by than 75 mg/dl/hr, by between 50 and 75 mg/dl/hr, or by less than 50 mg/dl/hr, respectively.[7]

Acidosis is usually corrected with intravenous fluid administration and insulin therapy alone.[2,4,12] Bicarbonate administration for correction of acidosis in humans with DKA is controversial.[12,16-18] The American Diabetes Association recommends bicarbonate supplementation only in patients with DKA in which arterial pH remains less than 7.0 after 1 hour of fluid therapy.[16] Risks associated with bicarbonate treatment in humans with DKA include exacerbation of hypokalemia, increased hepatic production of ketones, paradoxical cerebrospinal fluid acidosis, cerebral edema, and worsening intracellular acidosis due to increased production of carbon dioxide (also known as paradoxical cerebral acidosis).[12,17,18] Bicarbonate treatment is not needed in most dogs and cats with DKA.[2,4] However, a recent retrospective study of 127 dogs with DKA reported that the degree of acidosis was associated with poor outcome.[2] The same study reported that intravenous sodium bicarbonate therapy was also associated with poor outcome.[2] It is not known if bicarbonate therapy in itself, or the severe degree of acidosis that prompted such therapy, was the cause of poor outcome in dogs treated with bicarbonate.

One bicarbonate treatment protocol is to administer sodium bicarbonate at ½ to ⅓ of (0.3 × body weight × negative base excess) over a 20-minute interval every hour, while monitoring venous pH every hour. However, there are no studies to support this or any other bicarbonate treatment protocol in dogs and cats with DKA. The American Diabetes Association recommends treating pediatric patients with DKA who maintain a pH of less than 7.0 after 1 hour of fluid therapy with 2 mEq/kg sodium bicarbonate added to 0.9% sodium chloride, in a solution that does not exceed 155 mEq/L of sodium, over 1 hour.[16] The pH is monitored every hour and treatment is repeated until pH is 7.0 or greater.[16]

Table 67-2 Administration of IV Insulin in Patients With DKA*

Blood Glucose Concentration (mg/dl)	Fluid Composition	Rate of Administration (ml/hr)
>250	0.9% NaCl	10
200 to 250	0.45% NaCl + 2.5% dextrose	7
150 to 200	0.45% NaCl + 2.5% dextrose	5
100 to 150	0.45% NaCl + 5% dextrose	5
<100	0.45% NaCl + 5% dextrose	Stop fluid administration

DKA, Diabetic ketoacidosis; *IV,* intravenous; *NaCl,* sodium chloride.

Concurrent disease is believed to contribute to DKA. Therefore identification and treatment of concurrent disease are indicated. It is possible that the latter decreases glucagon secretion and contributes to improved diabetic regulation and resolution of DKA.

* Not to exceed 0.5 mEq/kg/hr without electrocardiographic monitoring.

* 2.2 U/kg of regular crystalline insulin added to 250 ml of 0.9 % NaCl solution. The administration set must be flushed with 50 ml of the mixture before administering the solution to the animal.

67.9 OUTCOME

Most dogs and cats (70%) treated for DKA survive to discharge from the hospital.[2,4] Median hospitalization time for dogs and cats with DKA is 6 and 5 days, respectively.[2,4] At least 7% of dogs and up to 40% of cats experience recurring episodes of DKA.[2,4] Dogs with coexisting hyperadrenocorticism are less likely to be discharged from the hospital, and the degree of base deficit in dogs is associated with outcome.[2]

67.10 SUGGESTED FURTHER READING*

KA Bruskiewicz, RW Nelson, EC Feldman, et al.: Diabetic ketosis and ketoacidosis in cats: 42 cases (1980-1995). *J Am Vet Med Assoc*. **211**, 1997, 188, *A detailed retrospective study of cats with DKA*.

DZ Hume, KJ Drobatz, RS Hess: Outcome of dogs with diabetic ketoacidosis: 127 dogs (1993-2003). *J Vet Intern Med*. **20**, 2006, 547, *A detailed retrospective study of dogs with DKA*.

DK McIntire: Treatment of diabetic ketoacidosis in dogs by continuous low-dose intravenous infusion of insulin. *J Am Vet Med Assoc*. **202**, 1993, 1266, *The first report of DKA treatment by way of an IV CRI of insulin in dogs, which has remained the gold standard since its publication*.

SE Parsons, KJ Drobatz, SV Lamb, et al.: Endogenous serum insulin concentration in dogs with diabetic ketoacidosis. *J Vet Emerg Crit Care*. **12**, 2002, 147, *A study documenting that endogenous insulin concentrations are detectable in most dogs with DKA and occasionally normal in some dogs with DKA*.

* See the CD-ROM for a complete list of references

68 Chapter 68 Hyperglycemic Hyperosmolar Syndrome

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68.1 KEY POINTS

- Hyperglycemic hyperosmolar syndrome (HHS) is a form of diabetic crisis marked by severe hyperglycemia (>600 mg/dl) and hyperosmolality with no or minimal urine ketones.
- Absence or resistance to insulin and increases in diabetogenic hormone levels stimulate glycogenolysis, and gluconeogenesis, hyperglycemia, osmotic diuresis, and dehydration result.
- Reduction of glomerular filtration rate (GFR) is essential to attain the severe, progressive hyperglycemia associated with HHS.
- Renal failure and congestive heart failure are common concurrent diseases. These likely contribute to HHS via effects on reduction of GFR.
- The most important goals of therapy are to replace fluid deficits and then slowly decrease the glucose concentration, thereby avoiding rapid intracranial shifts in osmolality and preventing cerebral edema. Fluid therapy will start to reduce blood glucose levels via dilution and by increasing GFR and subsequent urinary glucose excretion.
- Prognosis for HHS patients is poor, primarily as a result of concurrent disease.

68.2 INTRODUCTION

Nonketotic HHS is an uncommon form of diabetic crisis marked by severe hyperglycemia (>600 mg/dl), minimal or absent urine ketones, and serum osmolality more than 350 mOsm/kg.[1] Other names for this syndrome include *hyperosmolar hyperglycemic nonketotic state* and *hyperosmolar nonketotic coma*. These terms have been replaced by *hyperglycemic hyperosmolar syndrome* in human medicine to better reflect the variable degrees of ketosis and inconsistent incidence of coma that occur with this syndrome.[2,3] Coma appears to be an uncommon form of this syndrome in animals.

Hyperglycemic Hyperosmolar Syndrome (HHS) is an infrequent, albeit well documented, complication of diabetes mellitus.[4-7] The incidence in human diabetics has been estimated to represent less than 1% of all human diabetic hospital admissions.[3,8,9] In comparison, HHS accounted for 6.4% of total emergency room visits by diabetic cats in one retrospective study.[4] The incidence in dogs is unknown.

This chapter will review the pathogenesis, clinical findings, diagnostic evaluation, and treatment of HHS.

68.3 PATHOGENESIS

Pathogenesis of HHS involves hormonal alterations, reduction of glomerular filtration rate (GFR), and contributions from concurrent disease.

68.3.1 Hormonal Alterations

HHS begins with a relative or absolute lack of insulin coupled with increases in circulating levels of counterregulatory hormones including glucagon, epinephrine, cortisol, and growth hormone. These counterregulatory hormones are elevated in response to an additional stressor, such as concurrent disease. Epinephrine and glucagon inhibit insulin-mediated glucose uptake in muscle and stimulate hepatic glycogenolysis and gluconeogenesis, increasing circulating glucose concentration. Cortisol and growth hormone inhibit insulin activity and potentiate the effects of glucagon and epinephrine on hepatic glycogenolysis and gluconeogenesis. In conjunction with insulin deficiency, increases in the diabetogenic hormones increase protein catabolism, which in turn impairs insulin activity in muscle and provides amino acids for hepatic gluconeogenesis.[10] Pathogenesis of HHS is very similar to that of diabetic ketoacidosis, except that in HHS it is believed that small amounts of insulin and hepatic glucagon resistance inhibit lipolysis, thereby preventing ketosis[3,11,12] and instead promoting HHS. Lower levels of growth hormone have also been documented in patients with HHS.[12,13]

Hyperglycemia is the primary result of these hormonal alterations. It promotes osmotic diuresis, and osmotic diuresis increases the magnitude of the hyperglycemia, thus leading to a vicious circle of progressive dehydration and hyperosmolality. Neurologic signs are thought to develop secondary to cerebral dehydration induced by the severe hyperosmolality. In humans, elevated blood urea nitrogen (BUN) levels, acidemia, elevated sodium concentration and osmolality, but not glucose concentration, are correlated with the severity of neurologic signs.[14]

68.3.2 Reduction of Glomerular Filtration Rate

Osmotic diuresis, additional losses such as via vomiting, and decreased water intake contribute to progressive dehydration, hypovolemia, and ultimately a reduction in the GFR as the syndrome progresses. Severe hyperglycemia can occur only in the presence of reduced GFR, because there is no maximum rate of glucose loss via the kidney.[15,16] That is, all glucose that enters the kidney in excess of the renal threshold will be excreted in the urine. An inverse correlation exists between GFR and serum glucose in diabetic humans.[15] Reductions in GFR increase the magnitude of hyperglycemia, which exacerbates glucosuria and osmotic diuresis. Human HHS survivors have also shown a reduced thirst response to rising vasopressin levels, which may also contribute to dehydration[17] and decreased GFR.

68.3.3 Influence of Concurrent Disease

Concurrent disease is important for initiating the hormonal changes associated with HHS and can also be important for exacerbating hyperglycemia. Diseases that are thought to predispose previously stable diabetics to a diabetic crisis include renal failure, congestive heart failure (CHF), infection, neoplasia, and other endocrinopathies,[1,18] although any disease can occur. Pancreatitis and hepatic disease seemed to be uncommon concurrent diseases in cats with HHS.[4]

Renal failure and CHF also exacerbate the hyperglycemia associated with HHS because of their effects on GFR. Decreased GFR is inherent to renal failure. Inability to concentrate urine provides another source for obligatory diuresis. Myocardial failure, diuretic use, and third spacing of fluids associated with CHF may decrease GFR.

Cardiac medications such as β-blockers and diuretics are also known to alter carbohydrate metabolism, thus predisposing to diabetic crisis.[3]

68.4 HISTORY AND CLINICAL SIGNS

Animals diagnosed with HHS may be previously diagnosed diabetics receiving insulin or may be newly diagnosed at the time HHS is recognized. The most common client complaints are fairly nonspecific and include decreased appetite, lethargy, vomiting, and weakness. Owners may report polyuria, polydipsia, and polyphagia consistent with diabetes, although these clinical signs may have gone unrecognized. History may also reveal recent onset of neurologic signs including circling, pacing, mentation changes, or seizure. Weight loss is an inconsistent finding.

68.5 PHYSICAL EXAMINATION

Vital parameters (temperature, pulse, and respiration) and body weight vary considerably with severity of the syndrome and presence and chronicity of comorbid diseases. Hypothermia is not uncommon as the syndrome progresses. Dehydration, marked by decreased skin turgor, dry or tacky mucous membranes, sunken eyes, and possibly prolonged capillary refill time, are common findings on physical examination. Mentation changes are also common. Most animals are reported as being depressed, but severely affected patients may be obtunded, stuporous, or comatose. Additional neurologic abnormalities including weakness or ataxia, abnormal pupillary light reflexes or other cranial nerve abnormalities, twitching, or seizure activity may be noted. Plantigrade stance, especially in cats, may be present subsequent to unregulated diabetes mellitus.

Other findings in patients with HHS are dependent on coexisting diseases. Animals should be examined closely for signs of heart disease which may include any of the following: heart murmur, gallop, bradycardia, tachycardia or other arrhythmias, dull lung sounds, crackles, increased respiratory rate and effort, pallor, prolonged capillary refill time, and decreased blood pressure. Increased respiratory rate and effort may suggest cardiac failure but could also be secondary to infection, hyperosmolality, acidosis, asthma, or neoplasia. Animals with renal failure may have kidneys of abnormal size, oral ulceration, and pallor from anemia and may smell of uremia.

68.6 DIAGNOSTIC CRITERIA

The standard criteria for diagnosis of HHS in veterinary medicine are a serum glucose concentration greater than 292 600 mg/dl, absence of urine ketones, and serum osmolality greater than 350 mOsm/kg.[1] In humans, the criteria for 293 diagnosis of HHS require a serum glucose greater than 600 mg/dl, arterial pH over 7.3, serum bicarbonate greater than 15 mmol/L, effective serum osmolality greater than 320 mOsm/kg, and anion gap less than 12 mmol/L. In addition, humans with HHS may have small quantities of urine and serum ketones, measured by the nitroprusside method.[2,3]

Glucose concentrations can reach 1600 mg/dl in severely affected animals.[1] Blood glucose concentration may exceed the readable range on patient-side analyzers. Clinical suspicion for HHS should remain high in this situation and additional diagnostic methods should be instituted to better define the severity of hyperglycemia, state of diabetes, and presence of coexisting diseases. Measuring glucose is also vital to rule out hypoglycemia as a cause of neurologic signs.

Osmolality measured by freezing point depression is not a commonly available patient-side test. Estimated serum osmolality can be calculated using the following formula[19]:

$$\text{Serum osm}_{(\text{cak})} = 2(\text{Na}^{+} + \text{K}^{+}) + (\text{BUN} \div 2.8) + (\text{glucose} \div 18)$$

BUN and glucose are measured in mg/dl.

Because BUN equilibrates readily across cell membranes and effects of potassium on osmolality are small, calculating effective osmolality may be a better estimate[19]:

$$\text{Effective osm} = 2(\text{Na}^{+}) + (\text{glucose} \div 18)$$

BUN and glucose measured in mg/dl.

Normal serum osmolality is 290 to 310 mOsm/kg. Neurologic signs have been documented in animals when osmolality exceeds 340 mOsm/kg[20] (Box 68-1).

Urine ketones can be assessed quickly using urine dipsticks. If urine is not available, serum ketones may be assessed by placing a few drops of serum on urine dipsticks.

68.6.1 Additional Diagnostic Evaluation

Additional diagnostic parameters, including serum chemistry analysis (with precise glucose measurement), complete blood count, urinalysis, urine culture, and (venous) blood gas, should be pursued in patients with confirmed or suspected HHS. Blood cell count abnormalities are varied and nonspecific. The packed cell volume and total solids level may be high secondary to dehydration. Chemistry abnormalities are dependent on degree of dehydration and presence of underlying disease. The most common biochemical abnormalities in cats with HHS include azotemia, hyperphosphatemia, elevated aspartate transaminase, acidosis, elevated lactate concentration, and hypochloremia.[4] Azotemia may be prerenal or renal in origin.

68.6.1.1 Box 68-1 Important Calculations

Dehydration deficit:

Fluid deficit (ml) = body wt (kg) × % dehydration (as decimal) × 1000 (ml/L)

Osmolality:

$$\text{Serum osm}_{(\text{calc})} = 2(\text{Na}^{+} + \text{K}^{+}) + (\text{BUN} \div 2.8) + (\text{glucose} \div 18)$$

Effective osmolality:

$$\text{Effective osm} = 2(\text{Na}^{+}) + (\text{glucose} \div 18)$$

Corrected sodium:

$$\mathrm{Na}^{+}_{(\mathrm{corr})} = \mathrm{Na}^{+}_{(\mathrm{measured})} + 1.6([\text{measured glucose} - \text{normal glucose}] \div 100)$$

BUN, Blood urea nitrogen; *K^+,* potassium; *Na^+,* sodium; *osm,* osmolality. BUN and glucose measured in mg/dl.

Venous blood gas analysis should be used to assess the degree of acidemia. It is not possible to differentiate HHS from DKA in cats based on the degree of metabolic acidosis.[4] In HHS, metabolic acidosis is caused by accumulation of uremic acids and lactic acid, rather than ketones. Lactic acidosis is an indicator of poor tissue perfusion secondary to dehydration and hypovolemia.

Serum electrolytes should be monitored to help in choosing fluid therapy and to calculate the osmolality. Sodium concentration is the prime determinate of serum osmolality. In HHS, the true magnitude of sodium concentration will be masked by the hyperglycemia. Measured serum sodium is reduced by hyperglycemia-induced osmotic pull of water into the vasculature.[21]

Sodium level should be expected to rise as glucose levels return to normal. Calculating the corrected serum sodium value can give a better indication of severity of free water loss (see Box 68-1). For every 100 mg/dl increase in glucose above normal, the measured serum sodium decreases by 1.6 mEq/dl.[21] A corrected serum sodium level can be calculated using the following formula:

$$\mathrm{Na}^{+}_{(\mathrm{corr})} = \mathrm{Na}^{+}_{(\mathrm{measured})} + 1.6([\text{measured glucose} - \text{normal glucose}] \div 100)$$

Animals in diabetic crisis are classically expected to have low total body potassium concentrations,[1] although cats with HHS tend to have a normal serum potassium concentration.[4] Potassium losses are expected via diuresis, vomiting, and decreased intake; increases in potassium may occur secondary to acidosis, severe hyperosmolality,[22] insulin deficiency, and poor renal perfusion. Potassium levels are expected to decrease as acidosis improves and with insulin-induced cotransport of glucose and potassium into cells.

A thorough search for underlying disease should be undertaken in all patients with HHS. Additional diagnostic techniques including thoracic and abdominal radiographs, abdominal ultrasonography, echocardiogram, retroviral testing (cats), and endocrine testing (especially thyroid hormone levels in cats) may be indicated based on historical or physical findings or results of preliminary diagnostic results.

68.7 TREATMENT

Goals of therapy for patients with HHS include replacing the fluid deficit, slowly reducing serum glucose levels, addressing electrolyte abnormalities, and treating concurrent disease.[2]

To prevent exacerbation of neurologic signs, it is important not to lower the serum glucose or sodium too rapidly. Hyperosmolality induces formation of osmotically active idiogenic osmoles in the brain. These idiogenic osmoles protect against cerebral dehydration by preventing movement of water from the brain into the hyperosmolar blood.

Because idiogenic osmoles are eliminated slowly, rapid reduction of serum osmolality establishes an osmotic gradient across the blood-brain barrier, leading to cerebral edema and neurologic signs.[23]

The first goal of therapy is to replace dehydration deficits slowly using an isotonic crystalloid solution. Initially, 0.9% sodium chloride solution is the fluid of choice, because it will both address the fluid deficits and replace glucose with sodium in the extracellular space, thus preventing a rapid shift in osmolality. Hypernatremia should be corrected slowly with a decrease of no more than 1 mEq/L/hr.[24]

The fluid therapy plan should include dehydration deficit, ongoing losses and maintenance fluid needs (see Box 68-1). Fluid deficit (in ml) should be calculated by multiplying body wt (kg) × % dehydration (expressed as decimal) × 1000 (ml/L). On its own, fluid therapy will start to reduce blood glucose levels via dilution and by increasing GFR and subsequent urinary glucose excretion.[25] Ideally, the dehydration deficit should be replaced over 24 hours. Treating a patient with HHS and concurrent CHF presents a dilemma. Even maintenance amounts of parenteral fluids could be detrimental, so rehydration must be done more slowly and with care. Forced enteral fluid supplementation, as via a nasoesophageal tube, may be a viable option to aid in rehydration of some patients with CHF that are not vomiting.

Insulin should not be given until the hypovolemia and dehydration have improved. Unlike in DKA where insulin therapy is vital because of its role in reducing ketogenesis, insulin therapy is not as critical for resolution of HHS, because much of the syndrome can be improved just by correcting fluid deficit. Mechanics of insulin therapy for HHS are similar to those used in DKA, with protocol changes designed to lower the glucose levels more slowly. Using regular insulin as part of either intramuscular or intravenous protocols, at dosages 50% of those used for DKA, should prevent rapid decline in serum glucose.[1] Insulin therapy should be instituted after a minimum of 4 to 6 hours of fluid therapy and only if the potassium is at least 3.5 mmol/L. Intravenous constant rate infusion of 0.025 to 0.05 U/kg/hr can be made by adding 0.5 U/kg (cat) to 1 U/kg (dog) regular insulin to 250 ml 0.9% sodium chloride; the resulting solution should be started at 10 ml/hr via a dedicated intravenous line. For the intramuscular protocol, 0.1 U/kg of regular insulin should be given, followed by 0.05 U/kg q1-2h until the glucose is less than 300 mg/dl, then q4-6h. With both protocols, the goal is to decrease the glucose levels by no more than 50 to 75 mg/dl/hr.[2,26] If the glucose is dropping too rapidly, the insulin dosage should be decreased by 25% to 50%. If the glucose is less than 250 to 300 mg/dl, 5% dextrose should be added to the fluids. Regular insulin should be continued until the animal is eating. Once the animal is eating and drinking, long-acting insulin therapy, dietary management, and monitoring should be started as for a standard diabetic. Vigilant therapy and careful monitoring of concurrent diseases are essential.

68.8 MONITORING

Glucose should initially be measured every 1 to 2 hours, and ketones should be checked daily. Serial neurologic examinations should be performed to monitor for signs of cerebral edema. Potassium, phosphorus, and magnesium levels should be monitored at least once daily and supplemented in fluids as needed. Electrocardiogram, blood pressure, and central venous pressure may be helpful in monitoring patients with HHS. Multilumen central venous catheters will facilitate glucose and central venous pressure monitoring and administration of multiple infusions.

68.9 PROGNOSIS

The mortality rate for patients with HHS is high because of the severity of the syndrome as well as presence of concurrent disease. In humans, the mortality rate is consistently 15% to 17% of HHS admissions, and many outcome predictors have been identified.[14,27-29] There are no clear predictors of survival from HHS for animals. In one feline study, in-hospital mortality was 64.7% and long-term (>2 month) survival was only 12%.[4] Outcome was not predicted by presence of neurologic signs, serum glucose concentration, measured serum sodium concentration, corrected serum sodium concentration, or total and effective serum osmolality. Long-term survivors had curable concurrent diseases.

68.10

SUGGESTED FURTHER READING*

SP DiBartola: In *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 3, 2006, Saunders, St Louis, *Excellent review of electrolytes and acid-base physiology*.

EC Feldman, RW Nelson: In *Canine and feline endocrinology and reproduction*. ed 3, 2004, Saunders, St Louis, *The most comprehensive reference on small animal endocrinology. Excellent review of pathophysiology, clinical characteristics, and management of all forms of diabetes*.

A Koenig, K Drobatz, AB Beale, L King: Hyperglycemic, hyperosmolar syndrome in feline diabetics 17 cases (1995-2001). *JVECC*. **14**(1), 2004, 30–40, *A retrospective study evaluating clinical and laboratory findings and outcome in HHS cats*.

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* See the CD-ROM for a complete list of references

69 Chapter 69 Hypoglycemia

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69.1 KEY POINTS

- Normoglycemia is maintained by a balance between the glucose-lowering hormone insulin and glucose-elevating hormones glucagon, cortisol, epinephrine, and growth hormone.
- Hypoglycemia occurs via one of several mechanisms: inadequate dietary intake, excessive glucose utilization, dysfunctional glycogenolytic or gluconeogenic pathways or inadequate precursors for these pathways, or endocrine abnormalities.
- The most common causes of hypoglycemia include exogenous insulin overdose, hypoglycemia of puppies and toy breeds, sepsis, insulinoma and other insulin analog-secreting tumors, hypoadrenocorticism, and severe liver disease.
- Neuroglycopenia causes alterations in mentation, seizures, blindness or alterations in vision, somnolence, and weakness or ataxia.
- Adrenergic stimulation in response to declining blood glucose accounts for other common clinical signs of restlessness, anxiety, tachypnea, vomiting or diarrhea, and trembling.
- In hypoglycemic crises, parenteral dextrose administration is the most effective therapy. Food should be offered as soon as possible. Glucagon infusion may be used for cases of intractable hypoglycemia secondary to insulinoma or insulin analog-secreting neoplasms.

69.2 INTRODUCTION

Euglycemia is maintained by a balance of glucose production, storage, and release from storage forms. Many disease processes can interfere with normal glucose homeostasis and lead to hypoglycemia. This chapter will review normal glucose homeostatic mechanisms, clinical signs and causes of hypoglycemia, and treatment of a hypoglycemic crisis.

69.3 NORMAL GLUCOSE HOMEOSTASIS

Glucose comes from three sources: (1) intestinal absorption of glucose from digestion of carbohydrates; (2) breakdown of the storage form of glucose (glycogen) via glycogenolysis; and (3) production of glucose from precursors lactate, pyruvate, amino acids, and glycerol via gluconeogenesis. Glucose homeostasis is maintained by a balance between the glucose-lowering hormone insulin and glucose-elevating hormones, primarily glucagon, epinephrine, cortisol, and growth hormone.

Insulin is secreted by β-cells of the pancreas in response to the rising concentrations of glucose, amino acids, and gastrointestinal (GI) hormones (gastrin, secretin, cholecystokinin, and gastric inhibitory peptide) present after a meal.[1] Insulin inhibits gluconeogenesis and glycogenolysis, promotes glycogen storage, stimulates glucose uptake and utilization by insulin-sensitive cells, and decreases glucagon secretion. Insulin also promotes triglyceride formation in adipose tissue and the synthesis of protein and glycogen in muscle. Decreased levels of insulin stimulate gluconeogenesis and reduce glucose used by peripheral tissues.

As blood glucose concentrations fall, the counter-regulatory hormones glucagon, epinephrine, cortisol, and growth hormone are released. Both glucagon and epinephrine levels rise within minutes of hypoglycemia and have a transient effect on increasing glucose production; they subsequently support basal rates of glucose production.[2] Cortisol and growth hormone are released after a few hours, but their effects are also longer lasting.

Glucagon is secreted from pancreatic α-cells. It acts on the liver to stimulate glycogenolysis and, to a lesser extent, gluconeogenesis, thereby increasing hepatic glucose production. This is transient, however, and glucose production quickly declines toward basal rates as increasing levels of insulin counteract the effects of glucagon. Glucagon directly stimulates hepatic glycogenolysis and gluconeogenesis, mobilizes gluconeogenic precursors, and reduces peripheral glucose utilization. Epinephrine limits insulin secretion and increases glucagon secretion. Cortisol increases glucose-facilitating lipolysis and release of amino acids from muscle for gluconeogenesis in the liver. Growth hormone antagonizes effects of insulin by decreasing peripheral glucose utilization and promoting lipolysis.

Hypoglycemia results when glucose utilization exceeds glucose entry into circulation. General mechanisms of hypoglycemia include: (1) inadequate dietary intake, (2) excessive glucose utilization, (3) dysfunctional glycogenolytic or gluconeogenic pathways or inadequate precursors for these pathways, and (4) endocrine abnormalities. On its own accord, inadequate dietary intake is unlikely to cause hypoglycemia, because gluconeogenic and glycolytic pathways dominate during periods of fast. In most animals, a concurrent defect in one of the other mechanisms is required.

69.4 CLINICAL SIGNS AND CONSEQUENCES OF HYPOGLYCEMIA

Glucose is an obligate energy source for the brain. The brain has limited ability to use other substrates, can store minimal amounts of glycogen, and cannot manufacture glucose; therefore the brain relies on a constant stream of glucose for its energy needs.[3] Glucose enters the brain by facilitated diffusion. Adequate arterial glucose concentration is essential to maintaining a diffusion gradient. Because brain cells rely so heavily on glucose for 295 energy, neuroglycopenia, or hypoglycemia of the central nervous system (CNS), results primarily in 296 neurologic signs. The degree, rate of decline, and duration of hypoglycemia all contribute to type and severity of symptoms.

Neuroglycopenic signs occur as a direct result of CNS hypoglycemia. These include altered mentation or dullness, sleepiness, weakness or recumbency, ataxia, blindness or altered vision, and seizures.[2,4] Prolonged neuroglycopenia can lead to permanent brain injury and neurologic signs, especially blindness, that persist beyond resolution of the hypoglycemia. Neurogenic signs result from activation of the adrenergic system in response to the hypoglycemia. Humans describe being hungry, a tingling sensation, tremors or shakiness, a pounding heart, and anxiety or nervousness.[2] Similar signs noted in hypoglycemic dogs and cats include anxiety manifest as pacing, vocalizing or restlessness, and shaking or trembling.[4] Vomiting, anorexia, panting or tachypnea, diarrhea, and urination have been noted in hypoglycemic dogs and cats. Bradycardia and circulatory collapse have also been documented.[5] Signs may be episodic. Some animals, especially those with prolonged hypoglycemia, demonstrate no associated signs.[4] This hypoglycemia unawareness may occur in patients whose brains are induced by chronic or recurrent hypoglycemia to upregulate cerebral glucose uptake, thereby decreasing the perception of peripheral hypoglycemia by the brain.[3]

69.5 DIAGNOSIS OF HYPOGLYCEMIA

By definition, hypoglycemia is diagnosed by a blood glucose level of 60 mg/dl or less, although clinical signs often do not develop until the level is less than 50 mg/dl. Whipple's triad provides guidelines for identifying hypoglycemia: clinical signs consistent with hypoglycemia, a low blood glucose level, and abatement of signs with correction of the hypoglycemia.[2]

Hand-held glucometers tend to underestimate serum glucose.[6] Low glucose values obtained on a hand-held glucometer should be confirmed via other methods. Falsely low glucose values, or pseudohypoglycemia, can be obtained if the serum is not separated from the red blood cells within 30 minutes of collection, because the red blood cells continue to consume glucose for glycolysis.[7] If centrifugation and serum separation must be delayed longer than 30 minutes, collection in a sodium fluoride tube will arrest glycolysis.

Once hypoglycemia is identified, additional diagnostic modalities may be indicated to identify its etiology. Complete blood cell count, serum chemistry analysis, urinalysis, chest and abdominal radiographs, abdominal ultrasonography, insulin levels, and other endocrine testing may be indicated.

69.6 CAUSES OF HYPOGLYCEMIA

Many causes of hypoglycemia (Box 69-1) fall into the categories of excess insulin or insulin analog, inadequate glucose production, and excess cellular glucose consumption.

69.6.1 Excess Insulin or Insulin Analogs

69.6.1.1 Exogenous Insulin Overdose

Exogenous insulin overdose is possible in any animal receiving insulin therapy, whether for diabetes mellitus or for treatment of other disorders such as hyperkalemia or calcium channel blocker overdose. Insulin overdoses in diabetic animals occur more commonly in cats than dogs, in obese animals, and in cats receiving more than 6 units of insulin per injection.[4]

Anorexic or hyporexic diabetics receiving insulin are also at risk. Clinical signs are consistent with hypoglycemia. Treatment includes discontinuation of insulin therapy, feeding the animal as soon as possible, and administration of intravenous dextrose if the animal is too severely affected to eat. Duration of the hypoglycemia varies and is not necessarily dependent on the amount and type of insulin that caused the overdose.[4] Once the animal is stabilized and eating, the dextrose infusion can be tapered off while blood glucose levels continue to be monitored.

Some diabetic animals may not need insulin for several days, and others will become hyperglycemic more quickly. The animal should be monitored for onset of polyuria and polydipsia and hyperglycemia to verify need for insulin. Remission in transiently diabetic cats may be marked by a hypoglycemic episode. Once the need to restart insulin is confirmed, it is prudent to reduce the dosage by 25% to 50% initially and follow up with normal diabetic monitoring to attempt regulation.[8,9] There may be another underlying problem that predisposed the animal to hypoglycemia, and additional workup is warranted if hypoglycemia is ongoing or if the animal has additional history or signs unrelated to hypoglycemia.

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69.6.1.1.1

Box 69-1 Causes of Hypoglycemia

69.6.1.1.1.1

Artifact*

Pseudohypoglycemia*

Hand-held glucometer*

69.6.1.1.1.2

Excess Insulin or Insulin Analogues

Exogenous insulin overdose

Insulinoma

Paraneoplastic syndrome

- Hepatomas, hepatocellular carcinoma
- Leiomyomas, leiomyosarcomas
- Pulmonary, mammary, and salivary carcinoma
- Lymphoma, plasmacytoid tumors
- Oral melanoma, hemangiosarcoma

Toxins and medications

- Sulfonylureas
- Xylitol

69.6.1.1.1.3

Excess Glucose Utilization

Infection

- Sepsis

  - Babesiosis

- Exercise-induced (hunting dog) hypoglycemia
- Paraneoplastic
- Polycythemia
- Leukocytosis
- Pregnancy

69.6.1.1.1.4

Decreased Glucose Production

- Neonatal hypoglycemia
- Hepatic dysfunction
  - Portosystemic shunt
  - Inflammatory or infectious hepatitis
  - Hepatic lipidosis
  - Cirrhosis
  - Neoplasia
  - Glycogen storage disease
- Hypocortisolism
- Counterregulatory hormone deficiencies
  - Glucagon, growth hormone
  - Thyroid hormone, catecholamines

- Hypopituitarism

Glycogenic or gluconeogenic enzyme deficiencies

β-Blockers

*Cause of apparent, not true, hypoglycemia.

69.6.1.2 Insulinoma

Insulinomas are insulin-secreting, usually malignant, tumors of the pancreas. They are described more commonly in middle-aged to older dogs than in cats.[9–14] Patients often exhibit weakness or collapse, and severe hypoglycemia is an unexpected and isolated finding. Other clinical pathology data are generally unremarkable. Diagnosis is made by evaluating blood insulin concentration on a sample taken during an episode of hypoglycemia. High or sometimes normal insulin levels in the face of hypoglycemia is indicative of insulinoma. Some animals will have intermittent episodes of hypoglycemia and hyperinsulinemia that may require a supervised fast or multiple samples to identify.[15] Low fructosamine values may also lend support to a diagnosis.[16] If insulin levels are equivocal, an amended insulin-to-glucose ratio (AIGR) can be calculated.

$$\text{AIGR} = (\text{insulin} \times 100) \div (\text{plasma glucose} - 30).$$

A denominator of 1 is used if the plasma glucose is less than 30 mg/dl. An AIGR over 30 suggests insulinoma,[17] although is not definitive.[9] Abdominal ultrasonography may or may not reveal a mass or nodule in the pancreas. Computed tomography, scintigraphy, and surgical exploration are other options for attempted localization of insulinoma.[9,18–20]

Emergency treatment for symptomatic hypoglycemia is outlined below. The treatment of choice for insulinoma is surgical excision. Medical options for animals not undergoing surgery or for those with metastatic disease and persistent hypoglycemia include small frequent feedings of a food low in simple sugars and glucocorticoids (prednisone 0.5 to 1 mg/kg in divided doses PO q12 h[21]). Higher doses of glucocorticoids and diazoxide (10 mg/kg initially up to 60 mg/kg, divided q12 h[21]), which directly inhibits pancreatic insulin secretion, can be used in patients with refractory disease. Other adjunctive therapies include streptozocin[22] (which selectively destroys pancreatic β-cells), somatostatin analogs such as octreotide[23,24] (which suppress synthesis and secretion of insulin), or alloxan (a β-cell cytotoxin).[9]

Prognosis is guarded and depends on the extent of both disease and treatment. In one study, median survival time was 74 days for dogs with medical treatment only, and 381 days for dogs undergoing surgery.[25] In another study, median survival time was 18 months for dogs with disease confined to the pancreas and local lymph nodes, and less than 6 months for dogs with distant metastases.[10] Nelson and Feldman reported that 10% to 15% of dogs undergoing surgery died or were euthanized within 1 month of surgery, 25% died within 6 months, and 60% to 70% lived more than 6 months, with many living longer than 1 year and some even longer than 2 years.[9]

69.6.1.3 Paraneoplastic Hypoglycemia

Although any tumor can be associated with hypoglycemia, the most commonly described non–β-cell neoplasms associated with hypoglycemia include hepatomas and hepatocellular carcinoma, leiomyomas and leiomyosarcomas, and other carcinomas or adenocarcinomas (especially those of pulmonary, mammary, and salivary origin),[26] lymphoma, plasmacytoid tumors, oral melanoma, and hemangiosarcoma. Neoplasia can cause hypoglycemia via secretion of insulin or insulin-like peptides, accelerated consumption of glucose by the tumor cells, or by failure of glycogenolysis or gluconeogenesis by the liver. Historical and clinical findings and treatment are consistent with the specific tumor.

69.6.1.4 Toxins and Medications

Certain toxins have been associated with hypoglycemia in dogs and cats. Excessive dosages of oral glucose-lowering agents such as the sulfonylurea drugs chlorpropamide and glipizide may cause hypoglycemia. These drugs are thought to stimulate insulin secretion from the pancreas, enhance tissue sensitivity to insulin, and decrease basal hepatic glucose production.[21] Xylitol-sweetened products, such as sugar-free gum, can cause hypoglycemia in dogs via its stimulation of insulin release from β-cells.[27] β-Blockers, such as atenolol, are also thought to contribute to hypoglycemia via interference with adrenergic counterregulatory mechanisms.

A history of exposure or known ingestion coupled with consistent signs or low blood glucose levels would substantiate the diagnosis. In addition to treating hypoglycemia, induced emesis and activated charcoal administration may be indicated if the ingestion is identified early and the patient is not clinically impaired by hypoglycemia (see Chapter 77, Approach to Poisoning and Drug Overdose).

69.6.2 Inadequate Glucose Production

69.6.2.1 Hypoglycemia of Puppies and Toy Breeds

Most commonly, hypoglycemia of neonatal and pediatric animals stems from inadequate substrate for glycolysis or gluconeogenesis. Glycogen stores are small and easily depleted in the face of inadequate food intake. Hepatic enzyme systems may also be immature.[28] Additionally, the brain accounts for most of the basal metabolic rate in the neonate, thus contributing to the frequent development of hypoglycemia in the young. In the nursing puppy, factors predisposing to hypoglycemia include premature birth, debilitation of the bitch at parturition, being the runt of the litter, and diabetes in the bitch.[28] Toy or small breed dogs are also at risk. In the weaned puppy, factors predisposing to hypoglycemia include concurrent infection, vaccinations, vigorous exercise, GI upset, hypothermia, poor nutrition, and extended fast.[28] Most puppies and toy breeds respond readily to supplementation and increased feeding frequency. Recurrent or persistent hypoglycemia warrants further investigation. Other differentials for hypoglycemia that must be considered in a hypoglycemic puppy or kitten include portosystemic shunt or other hepatic disease, sepsis, glycogen storage disease, and counterregulatory hormone deficiency.

69.6.2.2 Hepatic Disease

Portosystemic shunt, glycogen storage disease, severe inflammatory or infectious hepatitis, hepatic lipidosis, cirrhosis, and hepatic neoplasia are specific etiologies of hepatic failure that can lead to hypoglycemia via dysfunctional glycogen storage, glycogenolytic, and gluconeogenic capabilities. Euglycemia usually is maintained until late in the course of hepatic disease until approximately 70% of hepatic function is lost.[7] Patients with portosystemic shunt and glycogen storage disease are usually young and may be small or unthrifty. Evaluation of an animal with severe liver disease may reveal a poor body condition score, microhepatica or enlarged liver, icterus, ascites, melena, vomiting, diarrhea, anorexia, or signs of hepatic encephalopathy such as depression or seizures. Clinical pathology data may show hypoalbuminemia, low blood urea nitrogen, hypocholesterolemia, hyperbilirubinemia, elevated liver enzyme activities, and low urine specific gravity (see Chapters 126, 127, and 146, Hepatitis and Cholangiohepatitis, Hepatic Failure, and Portosystemic Shunt Management, respectively).

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69.6.2.3 Hypocortisolism and Other Counterregulatory Hormone Deficiencies

Hypoadrenocorticism, specifically hypocortisolism, may lead to hypoglycemia via loss of cortisol-induced counter-regulatory mechanisms. History may include anorexia, vomiting, diarrhea, melena or hematochezia, weakness, and possibly polyuria and polydipsia. Physical examination may reveal dehydration, bradycardia, muffled heart sounds, poor pulse quality, hypotension, and shock. Clinical pathology evaluation may reveal lack of stress leukogram, azotemia, hypercalcemia, hyponatremia, hypochloremia, and hyperkalemia. Confirmation of hypocortisolism is via the adrenocorticotropic hormone stimulation test. Treatment includes physiologic doses of glucocorticoids, and either fludrocortisone acetate (Florinef) or desoxycorticosterone pivalate if mineralocorticoids are also deficient. Fluid therapy is required in Addisonian crisis (see Chapter 76, Hypoadrenocorticism).

Deficiencies in other hormones such as glucagon, growth hormone, thyroid hormone, and catecholamines can all lead to hypoglycemia due to interference with counterregulatory mechanisms designed to prevent hypoglycemia. These occur uncommonly.

69.6.3 Excess Glucose Utilization

Infection, extreme exercise, polycythemia or leukocytosis, and pregnancy can all lead to excessive cellular glucose consumption.

69.6.3.1 Infection

Sepsis is a common cause of hypoglycemia. Decreased intake, decreased hepatic function and, most significantly, non–insulin-mediated increased consumption play a role in sepsis-induced hypoglycemia. Increased glucose consumption is believed to be induced by inflammatory mediators, such as tumor necrosis factor, especially in macrophage-rich tissues such as the spleen, liver, and lungs.[29] Hypotension or hypoxemia may also induce excess glucose consumption via increases in anaerobic glycolysis.

Patients with sepsis will be extremely ill. Vasodilatory shock may be evident by injected mucous membranes and hypotension. Other clinical signs will depend on the type and location of infection. A complete workup and blood cultures are indicated (see Chapters 106 and 107, Sepsis and Septic Shock, respectively). Canine babesiosis is an infection specifically associated with hypoglycemia.[30,31] Hypoglycemia at admission is a poor prognostic indicator in canine babesiosis and may occur secondary to the same mechanisms as bacterial sepsis or by consumption of glucose by the parasites.

69.6.3.2 Exercise-Induced Hypoglycemia

Exercise-induced hypoglycemia, also called *hunting dog hypoglycemia,* is generally seen in lean hunting or working dogs engaging in vigorous exercise. Glucose utilization by muscle markedly increases during exercise and endogenous glucose production, via glycolysis and gluconeogenesis, increases to meet this demand.[2] This form of hypoglycemia is believed to occur secondary to glycogen depletion in the face of increased glucose utilization. Affected animals should be fed small amounts frequently during exercise or should discontinue working if hypoglycemia continues.

69.6.3.3 Polycythemia and Leukocytosis

Hypoglycemia in polycythemia occurs secondary to increased metabolism of glucose by the large red blood cell mass.[7] Massive leukocytosis can have the same effect.

69.7 TREATMENT OF HYPOGLYCEMIC CRISIS

Initial treatment for a symptomatic hypoglycemic patient, regardless of etiology, is usually intravenous dextrose. A bolus of 1 ml/kg of 50% dextrose (0.5 g/kg) can be diluted 1:2 to 1:4 and is then given intravenously over 5 minutes. This solution is hypertonic and can cause phlebitis. In the absence of intravenous access, such as in the home setting, Karo syrup, pancake syrup, or honey can be applied to the oral mucous membranes.

Marked improvements in neuroglycopenic signs usually are seen within 1 to 2 minutes of supplementation. If the patient is alert and it is not contraindicated, the animal should be offered small frequent meals that are low in simple sugars. Otherwise, a constant rate infusion (CRI) of 2.5% to 5% dextrose should be administered until the cause of the hypoglycemia is identified and resolved. Dextrose infusions should be formulated by adding the appropriate amount of 50% dextrose to an isotonic fluid such as lactated Ringer's solution or 0.9% saline. Dextrose 5% in water should not be used as the sole fluid for hypoglycemia treatment, because it can result in severe, possibly life-threatening electrolyte abnormalities. Blood glucose should be monitored frequently to assess response to therapy. If a solution containing greater than 5% dextrose is needed to maintain blood glucose concentrations, it should be administered via a central line.

Care should be taken using intravenous dextrose in animals with suspected insulinoma or other tumors secreting insulin-like analogs. In these patients, a bolus of intravenous dextrose can stimulate release of even more insulin from the tumor, leading to a vicious cycle of dextrose infusion followed by rebound hypoglycemia. Additionally, hyperinsulinemia has been shown to depress glucagon secretion in humans, thus removing one of the counterregulatory mechanisms vital to maintaining euglycemia.[32] Glucagon CRI is another option for treating animals with insulin or insulin-like peptide-secreting tumors that are in a hypoglycemic crisis.[33] Glucagon is reconstituted according the manufacturer's instructions and diluted in 0.9% saline. This resulting 1000 ng/ml solution is first administered as a bolus of 50 ng/kg followed by a CRI of 5 to 40 ng/kg/min,[21] the lowest rate necessary to maintain low normal euglycemia.

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69.8 SUGGESTED FURTHER READING*

EC Feldman, RW Nelson: In *Canine and feline endocrinology and reproduction*. ed 3, 2004, Saunders, St Louis, *The most comprehensive reference on small animal endocrinology. Excellent review of pathophysiology, clinical characteristics, and treatment of all forms of diabetes*.

DK McIntire: Diabetic crises: insulin overdose, diabetic ketoacidosis, and hyperosmolar coma. *Vet Clin North Am Small Anim Pract*. **25**, 1995, 639, *Good review of clinical characteristics and treatment of diabetic crises*.

AS Moore, RW Nelson, CJ Henry, et al.: Streptozocin for treatment of pancreatic islet cell tumors in dogs: 17 cases (1989–1999). *J Am Vet Med Assoc*. **221**, 2002, 811, *Prospective study evaluating safety and efficacy of streptozocin*.

G Wess, C Reusch: Evaluation of five portable blood glucose meters for use in dogs. *J Am Vet Med Assoc*. **216**, 2000, 203, *Systematic evaluation of glucometer reliability*.

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* See the CD-ROM for a complete list of references

70 Chapter 70 Diabetes Insipidus

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70.1 KEY POINTS

- Diabetes insipidus results from a lack of secretion of or a lack of an appropriate renal response to a hormone known as *vasopressin* or *antidiuretic hormone*.
- Primary diabetes insipidus is most commonly acquired and central in origin. Common causes include trauma and intracranial masses.
- Secondary diabetes insipidus is usually renal in origin. Common causes include hypercalcemia, gram-negative sepsis, and severe hypokalemia.
- The manifestation of diabetes insipidus that requires emergency intervention is severe hypernatremia and dehydration caused by urinary free water losses without appropriate intake.
- The water deprivation test does provide valuable diagnostic information and can be dangerous, resulting in severe dehydration and hypernatremia.

70.2 INTRODUCTION

By definition diabetes *insipidus* is the tasteless or nonsweet diabetes. This differentiates it, of course, from the sweet diabetes, the better known diabetes *mellitus*. Diabetes insipidus is caused by a lack of the hormone vasopressin (otherwise known as *antidiuretic hormone* or *ADH*), a lack of renal receptors to vasopressin, or an inability of those receptors to respond to vasopressin. The presence of vasopressin and its ability to activate renal receptors are crucial to the kidneys' urine concentration capabilities. Vasopressin is a nonapeptide (nine amino acids) composed of six amino acids in a disulfide ring and three amino acids in a tail. In small animals the eighth amino acid in vasopressin is arginine, sometimes also called *AVP* or *arginine vasopressin*. [1]

70.2.1 Urine Concentration Mechanism

In a normally functioning kidney, as the solute within the tubule travels through the thick ascending loop of Henle, sodium (and subsequently chloride) is extracted by an energy-requiring ion pump from the solute in an area that is impermeable to water. This unusual feat renders the remaining solute hyposthenuric, or of lower osmolality than serum. The final urine concentration then depends on the presence and function of vasopressin. When the presence and/or function of vasopressin is lacking (diabetes insipidus), the final urine concentration will remain hyposthenuric, or perhaps isosthenuric or mildly hypersthenuric with partial disease.

70.2.2 Vasopressin Secretion and Sodium Homeostasis

Whole body water and sodium concentrations are kept constant despite a huge variability in dietary sodium intake and hydration status. Much of this control is due to vasopressin release from the neurohypothesis. The neurohypothesis consists of hypothalamic nuclei that secrete oxytocin and vasopressin. Following the nuclear synthesis of these hormones they are transported in their axons and finally secreted from the termini in the posterior lobe of the pituitary gland. Important stimuli for vasopressin release include low arterial blood pressure sensed by low-pressure receptors located in the heart and arterial vasculature, increased osmolality as sensed by central nervous system osmoreceptors, and increased angiotensin II levels.[2]

70.2.3 Antidiuretic Effects of Vasopressin

The antidiuretic effects of vasopressin occur in response to the binding of vasopressin to its receptor on the cells of the distal tubule and collecting duct. These are V_2 cyclic adenosine monophosphate-dependent receptors, which when activated cause an increase in water permeability of the luminal membrane by the insertion of aquaporin-2 water channels in the apical membrane of the renal epithelial cells. This allows a more rapid passive flow of water from the lumen through the epithelial cells and into the solute rich, concentrated interstitium, causing a rapid and marked increase in osmolality within the tubular lumen.[3] Theoretically the maximum urine concentration of a given animal would be equal to the maximum solute concentration of the medullary interstitium. Thus in times of hypernatremia due to excess salt intake or, more commonly, free water loss, resulting in a free water deficit or a hyperosmolar contraction of the extracellular space, the secretion of vasopressin causes an increase of water reabsorption from the kidney, a decrease in water excretion, and the normalization of sodium concentration.

70.3 CENTRAL DIABETES INSIPIDUS

Central diabetes insipidus (CDI) is the most common primary cause of diabetes insipidus. It is caused by a complete or partial lack of secretion of vasopressin from the axon termini in the anterior lobe of the pituitary gland. Documented causes of CDI in small animals include neoplastic, traumatic, inflammatory, congenital, and idiopathic conditions.[4,5] Glucocorticoid administration is thought to decrease vasopressin release in dogs, and therefore can be included in the causes of canine acquired CDI.[1]

In humans CDI is associated most commonly with brain surgery, trauma, and immune-mediated disease. Neoplasia, infectious disease, and hereditary disorders are also relatively common in this population.[6] Following brain trauma, at least 25% of long-term survivors suffer from what is defined in humans as *posttraumatic hypopituitarism.* [7] This syndrome most often includes suppression of hormone release from the anterior pituitary gland, but can also include decreased vasopressin secretion from the posterior pituitary gland. Posttraumatic CDI is thought to resolve within a few days in most human cases[8] but may also be a sign of permanent or late brain damage. Postsurgical CDI may be the most common cause in humans. As intracranial surgery, including hypophysectomies, and better care of head trauma become more and more common in small animal practice, veterinary intensive care units will likely experience more of these cases, as well. In humans pituitary gland radiation therapy can cause long-lasting pituitary gland damage with hormonal deficiencies. Interestingly, these rarely, if ever, include CDI. In dogs, there are no large case series reporting the most common causes of CDI. Documented causes have included traumatic,[9] neoplastic, and idiopathic conditions[4] and have occurred secondary to iatrogenic steroid administration or hyperadrenocorticism.[1]

70.4 NEPHROGENIC DIABETES INSIPIDUS

Nephrogenic diabetes insipidus (NDI) is caused by the failure of the kidney to respond to vasopressin. It is commonly divided into primary and secondary causes. Although primary NDI is uncommon and often congenital, secondary NDI is extremely common and likely the most common cause of diabetes insipidus seen in veterinary practice and intensive care units.

Primary NDI is most often hereditary in humans. Early diagnosis of this condition in humans through genetic screening has allowed for better care and increased survival. Most humans with congenital NDI have the X-linked form, causing the disease to manifest almost exclusively in male children.[10] In small animal patients primary or congenital NDI has been documented in a few rare reports in young dogs, never in cats. The canine reports included a Miniature Poodle, a German Shepherd, and a family of Huskies.[1]

By far the more common form of NDI in human[11] and veterinary patients is the acquired form. A partial list of causes of acquired NDI is included in Box 70-1. This syndrome is commonly seen in the emergency or critical care setting, caused by conditions such as pyometra or other causes of gram-negative sepsis, hypercalcemia, hypokalemia, liver failure, and hypoadrenocorticism. Each of these conditions causes an inability of the vasopressin to effectively bind and activate its receptor. In gram-negative sepsis bacterial endotoxins, especially from *Escherichia coli,* are thought to compete with vasopressin for binding sites on the tubular cell membranes, resulting in marked polyuria and polydipsia, and possibly hypernatremia if water intake is insufficient. Similarly, hypercalcemia and severe hypokalemia are thought to interfere with vasopressin binding and subsequent activation of the V_2 receptor.

Another common mechanism of secondary NDI is the abolition of the medullary hypertonicity gradient. As mentioned previously the presence and proper function of vasopressin and its receptors allow water channels to be open in the tubular cells of the collecting duct. The passage of water, then, from the tubular lumen into the interstitium is still passive and based on the hypertonicity of the renal medulla, enabled by the renal counter-current mechanism. If this hypertonicity, a condition referred to as *medullary washout,* is absent the urine will not become concentrated; it will be isosthenuric or even hyposthenuric. Medullary washout occurs in small animal patients for two common reasons:

1. Washout results from large amounts of urine passing through the tubules. This can occur in severely polyuric and polydipsic animals, such as dogs with hyperadrenocorticism or dogs and cats receiving high volumes of intravenous fluids for extended periods.
2. The solutes necessary to produce the medullary hypertonicity gradient are lacking, such as insufficient urea in dogs and cats with hepatic insufficiency or insufficient sodium in dogs with hypoadrenocorticism. In both instances these animals may be severely polyuric and have a functional secondary NDI, despite absolutely normal renal function and normal vasopressin concentrations.

70.5 DIAGNOSING DIABETES INSIPIDUS

Diabetes insipidus should be high on the differential diagnosis list for any dog or cat with severe polyuria and 300
polydipsia, especially when the urine is hyposthenuric. The first step in the diagnosis of primary diabetes insipidus 301
is to exclude most other common causes of polyuria and polydipsia. This can be accomplished by evaluating the signalment and complaint, a complete history, physical examination, a serum biochemistry profile, and a complete urinalysis and urine culture.

70.5.1

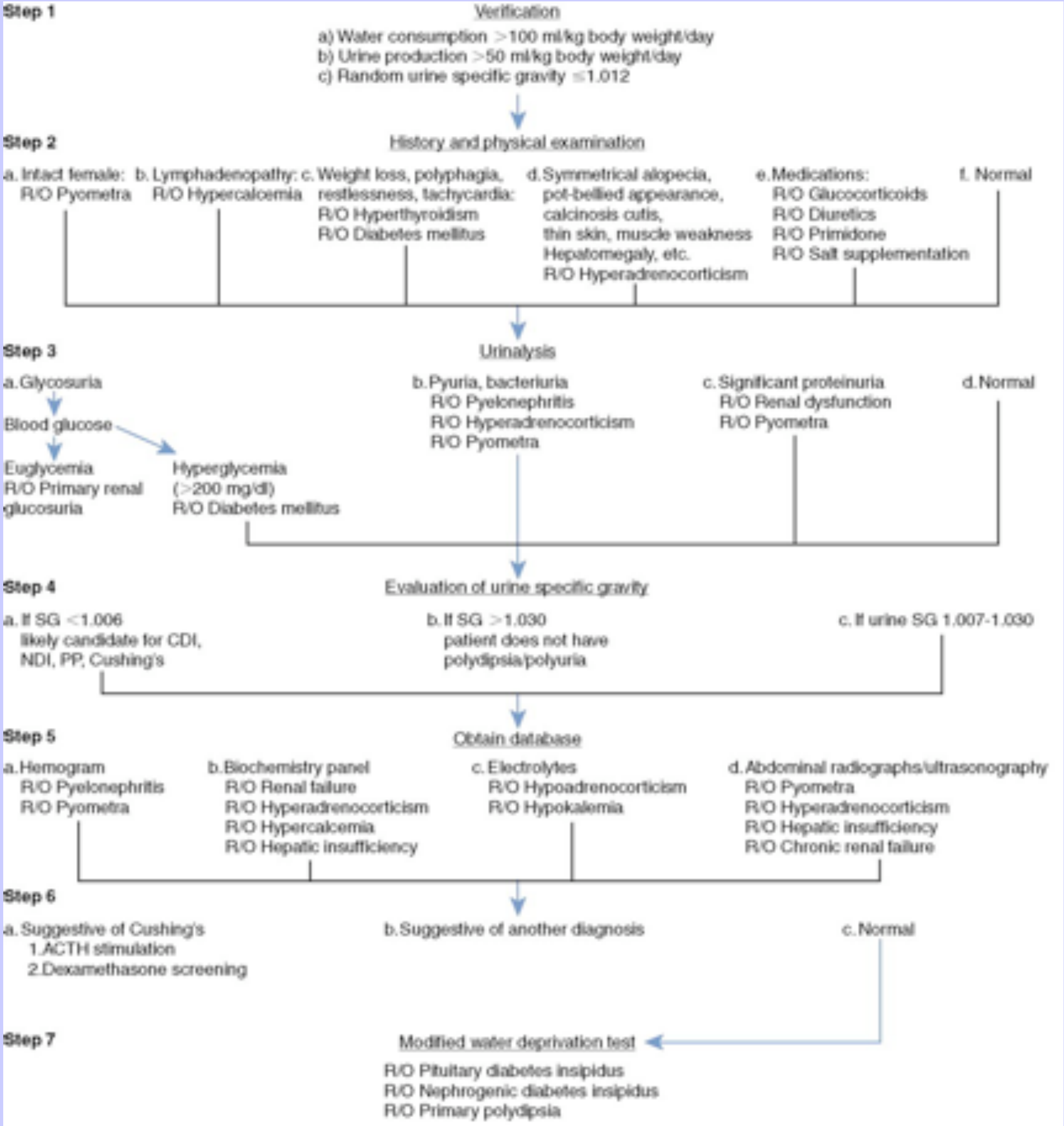
Box 70-1 Common Causes of Secondary Nephrogenic Diabetes Insipidus in Dogs and Cats

- Hypercalcemia
- Hypokalemia
- Pyelonephritis
- Pyometra and gram-negative sepsis
- Portal systemic shunts
- Liver insufficiency
- Hypoadrenocorticism (more common in dogs)
- Hyperthyroidism (more common in cats)

Normal serum biochemistry results would rule out many causes of secondary NDI, including hypercalcemia, severe hypokalemia, low serum urea concentrations associated with liver disease, and low sodium concentrations associated with Addison's disease. Normoglycemia would rule out diabetes mellitus and a cause of polyuria and polydipsia. Normal urinalysis results and negative urine culture findings would exclude diabetes mellitus and primary renal glycosuria, and would make pyelonephritis much less likely (Figure 70-1).

Additional testing may also be necessary when appropriate, including preprandial and postprandial serum bile acid concentrations to further exclude liver disease, serum T_4 concentrations to exclude hyperthyroidism, and imaging. Chronic kidney disease as a cause of polyuria and polydipsia is unlikely if the urine is hyposthenuric. If the urine is consistently isosthenuric, with normal or high-normal serum concentrations of blood urea nitrogen and creatinine, then a glomerular filtration study may be necessary to definitively rule out chronic kidney disease.

Figure 70-1 The diagnostic plan in a dog or cat with severe polydipsia and polyuria. *ACTH*, Adrenocorticotropic hormone; *CDI*, central diabetes insipidus; *NDI*, nephrogenic diabetes insipidus; *PP*, primary (psychogenic) polydipsia; *R/O*, rule out (a diagnosis); *SG*, specific gravity. From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, ed 3, St Louis, 2004, Saunders.


Step 1
Verification
a) Water consumption >100 ml/kg body weight/day
b) Urine production >50 ml/kg body weight/day
c) Random urine specific gravity ≤1.012
Step 2
History and physical examination
a. Intact female: R/O Pyometra
b. Lymphadenopathy: R/O Hypercalcemia
c. Weight loss, polyphagia, restlessness, tachycardia: R/O Hyperthyroidism R/O Diabetes mellitus
d. Symmetrical alopecia, pot-bellied appearance, calcinosis cutis, thin skin, muscle weakness Hepatomegaly, etc. R/O Hyperadrenocorticism
e. Medications: R/O Glucocorticoids R/O Diuretics R/O Primidone R/O Salt supplementation
f. Normal
Step 3
Urinalysis
a. Glycosuria
Blood glucose
Euglycemia R/O Primary renal glucosuria
Hyperglycemia (>200 mg/dl) R/O Diabetes mellitus
b. Pyuria, bacteriuria R/O Pyelonephritis R/O Hyperadrenocorticism R/O Pyometra
c. Significant proteinuria R/O Renal dysfunction R/O Pyometra
d. Normal
Step 4
Evaluation of urine specific gravity
a. If SG <1.006 likely candidate for CDI, NDI, PP, Cushing's
b. If SG >1.030 patient does not have polydipsia/polyuria
c. If urine SG 1.007-1.030
Step 5
Obtain database
a. Hemogram R/O Pyelonephritis R/O Pyometra
b. Biochemistry panel R/O Renal failure R/O Hyperadrenocorticism R/O Hypercalcemia R/O Hepatic insufficiency
c. Electrolytes R/O Hypoadrenocorticism R/O Hypokalemia
d. Abdominal radiographs/ultrasonography R/O Pyometra R/O Hyperadrenocorticism R/O Hepatic insufficiency R/O Chronic renal failure
Step 6
a. Suggestive of Cushing's 1. ACTH stimulation 2. Dexamethasone screening
b. Suggestive of another diagnosis
c. Normal
Step 7
Modified water deprivation test
R/O Pituitary diabetes insipidus
R/O Nephrogenic diabetes insipidus
R/O Primary polydipsia

A relatively common scenario we are faced with is an older dog with severe polyuria, polydipsia, and hyposthenuric urine, and no abnormal findings on a physical examination, a complete blood count, serum biochemistry profile, urinalysis (except the hyposthenuria), urine culture, and abdominal radiographs or ultrasonography. At this point in our diagnostic workup, the most likely remaining causes of the severe polyuria and polydipsia in this dog are hyperadrenocorticism, CDI or NDI, and primary or psychogenic polydipsia. The latter is a condition which is sometimes referred to as *psychogenic diabetes insipidus,* in which a dog drinks excessively for no apparent physiologic reason. Often these dogs are thought to drink this way because they are bored, stressed, or perhaps just enjoy drinking water.

The next step in the diagnosis is to attempt to exclude hyperadrenocorticism and psychogenic polydipsia. The first can be deemed much less likely based on a urine cortisol-to-creatinine ratio within the reference range or a low-dose dexamethasone suppression test with results within the reference range. An adrenocorticotropic hormone stimulation test is a less advisable option for this purpose, because in many dogs with hyperadrenocorticism the results of an adrenocorticotropic hormone stimulation test lie within the normal reference range. It is absolutely essential to make every effort to exclude hyperadrenocorticism in these cases. If this step is missed and a water deprivation test or desmopressin acetate trial is used to confirm CDI, a misdiagnosis may occur. Dogs with hyperadrenocorticism may appear to have CDI per results of these tests, and therefore will be mistakenly treated with desmopressin acetate instead of the proper diagnosis and treatment of their hyperadrenocorticism.

A random serum osmolality test may be used to attempt to diagnose psychogenic polydipsia. In this case dogs drink excessively as their primary disturbance and as a consequence are also polyuric. This is in contrast to diabetes insipidus, hyperadrenocorticism, and other causes or polyuria and polydipsia in which the primary disturbance is excessive urination. The polydipsia then, in these dogs, is an attempt to remain hydrated or to “catch up” with their urination. Theoretically the dogs with primary or psychogenic polydipsia should always be slightly overhydrated (with a low serum sodium concentration and low serum osmolality), and dogs with other causes of polyuria and polydipsia including diabetes insipidus should be slightly dehydrated (with a relatively high serum sodium concentration and serum osmolality).

On a random serum osmolality assay a result of less that 280 mOsm/L would be most consistent with psychogenic polydipsia. A result greater than 280 mOsm/L is hard to interpret, because even if the dog did have psychogenic polydipsia, if it did not drink excessively that day (possibly due to the visit to the veterinarian), the osmolality could be over 280 mOsm/L. If the random serum osmolality was indeed over 280 mOsm/L, an additional test to confirm the diagnosis of primary diabetes insipidus and to differentiate between the more common CDI and the rare primary NDI is warranted. Two options are available to achieve these goals, a modified water deprivation test and a desmopressin acetate (synthetic vasopressin) trial.

70.5.2 Modified Water Deprivation Test

A modified water deprivation test is based on the premise that a dog that truly suffers from diabetes insipidus will not be able to concentrate its urine even under conditions of moderate dehydration. This is because of either a lack of vasopressin (CDI) or lack of an appropriate renal response to vasopressin (NDI). An appropriate rise in urine specific gravity while dehydrated would be suggestive of psychogenic polydipsia. Once dehydration has been achieved without an appropriate rise in urine concentration, desmopressin is given intramuscularly. A marked increase in urine specific gravity at that time would be diagnostic for CDI, and a complete lack of response to desmopressin would be suggestive of NDI. Although in many cases this test does provide a definitive diagnosis of diabetes insipidus, we do not recommend its routine use. This is because many problems and possible misdiagnoses are associated with the analysis of the test results and, more importantly, grave risks can be associated with this test including severe dehydration, hypernatremia, and even death.[1]

70.5.2.1 Problems and Risks

70.5.2.1.1 Causes of Misdiagnoses

1. Medullary washout may occur. If the medullary interstitium has been "washed out" of solutes because of chronic severe polyuria and polydipsia for any reason, no urine concentration will occur despite the presence of endogenous vasopressin, desmopressin, and intact renal V_2 receptors. These dogs are then mistakenly diagnosed as suffering from NDI. The modified water deprivation test protocol attempts to eliminate this problem by recommending mild water restriction for a number of days before the test. Although helpful, this does not always eliminate the problem, is not always possible, and can be dangerous if dehydration is induced at home without proper monitoring.

2. Partial CDI, or a relative lack of vasopressin, can be very hard to diagnose, because a rise in urine specific gravity will be induced by dehydration. This rise, though, will be of inappropriately low magnitude, a very subjective value, and these dogs can be misdiagnosed as having psychogenic polydipsia. An additional rise in urine specific gravity should occur after desmopressin is given. Their response should be more dramatic, though, than in dogs with psychogenic polydipsia. This is a subjective value, making a definitive diagnosis of partial CDI very difficult.

3. Dogs with hyperadrenocorticism may appear to have CDI or partial CDI per a water deprivation test, leading to a misdiagnosis. This underlines the importance of establishing or excluding a diagnosis of hyperadrenocorticism in dogs before administering this test.

70.5.2.1.2 Associated Risks

The main and most important risk, and the reason why we do not recommend the routine use of this test, is severe dehydration than can be associated with acute severe hypernatremia. This occurs in cases of CDI or NDI when dehydration continues past 5% of body weight because of a lack of intensive monitoring. In cases of complete diabetes insipidus this could happen in a very short time (a few hours). This may be accompanied with a rapid rise in serum sodium concentrations resulting in neurologic symptoms. Despite aggressive fluid therapy, normal sodium concentrations may be difficult to restore. Desmopressin therapy is warranted in this case to slow the free water loss associated with the marked polyuria and to allow normalization of serum sodium concentrations.

Prevention of this complication includes only mild water deprivation at home during the days before the test, as well as aggressive monitoring of body weight, serum sodium, urea nitrogen, and creatinine frequently (at least hourly) during the test. The test should be stopped at 5% loss of body weight or any marked increase in the above serum values. Water, intravenous fluids (an intravenous catheter should be preplaced), and desmopressin should be available for immediate use.

70.5.3 Desmopressin Acetate Trial

The other diagnostic option available for the diagnosis of diabetes insipidus is the desmopressin acetate trial. 302

Although this test does not yield immediate results, it is a much safer option for most dogs than the modified 303 water deprivation test. This test is performed at home by the owner. The owner is instructed to collect urine, first thing in the morning, for a few days; to slightly limit access to water, if possible, for a few days; and then to begin therapy with desmopressin.

On days 5, 6, and 7 of this therapy urine is again collected first thing in the morning. All urine should be refrigerated after collection. At the end of the trial the urine samples are brought to the veterinarian for specific gravity measurement or, ideally, osmolality assays. The owners are encouraged to measure water intake during the trial, if possible.

The theory behind this therapeutic trial is that given mild water deprivation and desmopressin, the dog's urine concentration will steadily increase over the trial period. Medullary washout will be eliminated slowly if it was present initially, and a dog with CDI should have a marked increase in urine concentration. No increase in urine concentration by the end of the trial would be consistent with NDI or psychogenic polydipsia. Because primary NDI is so uncommon in an adult dog, this is usually not a big problem. A definitive differentiation between those two conditions would require a modified water deprivation test.

70.5.4 Imaging Following a Diagnosis of CDI

An extremely high percentage of adult dogs with acquired CDI appear to have intracranial mass lesions identifiable with magnetic resonance or computed topography imaging.[4] Such imaging is therefore recommended following the diagnosis of CDI, and radiation therapy is recommended if a lesion is identified.

70.6 Treatment of Diabetes Insipidus

A list of treatment options for CDI and NDI is included in Box 70-2. Most commonly CDI (partial or complete) is treated with desmopressin (oral or human nasal preparation given as eye drops). This treatment is extremely effective and when given consistently will enable the dog to concentrate urine normally. Other therapies can also be used in those with CDI as well as those with NDI. These include therapies aimed at lowering total body sodium and commonly include thiazide diuretics and salt-restricted diets. These therapies typically have minimal success in those with NDI.

Another option for owners of pets suffering from CDI or NDI is not to treat. Theoretically, as long as these animals are allowed free access to water, allowed to urinate outside, and are kept in conditions that help prevent dehydration through additional fluid loss (shade, no strenuous exercise in warm conditions), they will remain hydrated and may exhibit no clinical signs. This is especially important because of the high cost of desmopressin therapy for dogs with CDI and the lack of effective therapy for dogs with NDI.

70.6.1 Emergency Treatment

The most challenging aspect of this condition to an emergency or critical care clinician is the treatment of the severe dehydration, ongoing free water losses, and marked hypernatremia associated with small animals suffering from diabetes insipidus (primary or secondary) that for some reason have not had adequate access to water. This can be a result of vomiting or adipsia from an additional disease process, water deprivation by the owner (because of a belief that this will prevent urination in the house, or accidentally), the pet being lost without water, and animals that have sustained trauma (e.g., dog with diabetes insipidus that has been hit by a car and is presented in for veterinary care hours or days later). In these instances the clinician is presented with a patient with inappropriately high free water losses, dehydration, and high sodium concentrations. The first challenge is recognition of this state by the clinician, and then aggressive medical therapy. Aggressive therapy includes fluids, therapy for acute or chronic hypernatremia, and possibly desmopressin. Desmopressin therapy (injectable or eye drops) should be considered when dehydration and hypernatremia persist despite appropriate fluid therapy, urine volumes are high, and urine concentration is inappropriately low for the degree of clinical dehydration (see Chapter 54, Sodium Disorders).

70.6.1.1

Box 70-2 Therapies Available for Polydipsic/Polyuric Dogs With CDI, NDI, or Primary (Psychogenic) Polydipsia

A Central diabetes insipidus (severe)

  1 DDAVP (desmopressin acetate)

    a Effective

    b Expensive

    c May require drops in conjunctival sac if oral is ineffective

  2 LVP (lypressin [Diapid])

    a Short duration of action; less potent than DDAVP

    b Expensive

    c Requires drops into nose or conjunctival sac

  3 No treatment—provide continuous source of water

B Central diabetes insipidus (partial)

  1 DDAVP

  2 LVP

  3 Chlorpropamide

    a 30% to 70% effective

    b Inexpensive

    c Pill form

    d Takes 1 to 2 weeks to obtain effect of drug

    e May cause hypoglycemia

  4 Clofibrate—untested in veterinary medicine

  5 Thiazides

    a Mildly effective

- b Inexpensive
- c Pill form
- d Should be used with low-sodium diet

6 Low-sodium diet

7 No treatment—provide continuous source of water

C Nephrogenic diabetes insipidus

1 Thiazides—as above

2 Low sodium diet

3 No treatment—provide continuous source of water

D Primary (psychogenic) polydipsia

1 Water restriction at times

2 Water limitation

3 Behavior modification

- a Exercise
- b Another pet
- c Larger living environment

From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction*, ed 3, St. Louis, 2004, Saunders.

70.7 PROGNOSIS

The prognosis for dogs with CDI is good if they respond to therapy. Unfortunately, because of an apparently high incidence of intracranial masses in these dogs, the prognosis must remain guarded until advanced imaging can be pursued. The prognosis for dogs with primary NDI is guarded because of the lack of therapy for this condition. The prognosis for dogs with severe dehydration and hypernatremia is guarded, as well, especially if the condition is chronic. Proper medical therapy can often induce complete resolution of these complications and allow long-term medical treatment of CDI or the primary cause of secondary NDI.

70.8 SUGGESTED FURTHER READING*

EC Feldman, RW Nelson: Water metabolism and diabetes insipidus. In EC Feldman, RW Nelson (Eds.): *Canine and feline endocrine and reproduction*. 2004, Mosby, St Louis, *An excellent comprehensive chapter on diabetes insipidus, including normal and pathophysiology, differential diagnosis, clinical signs, a diagnostic approach, and treatment.*

S Ghirardello, C Malattia, P Scagnelli, M Maghnie: Current perspective on the pathogenesis of central diabetes insipidus. *J Pediatr Endocrinol Metab*. **18**, 2005, 631, *An interesting review of the causes of CDI in humans, with many aspects relevant to the advanced critical care veterinary practice*.

MF Harb, RW Nelson, EC Feldman, et al.: Central diabetes insipidus in dogs: 20 cases (1986-1995). *J Am Vet Med Assoc*. **209**, 1996, 1884, *The largest case series of dogs with CDI published to date. It includes interesting findings and the causes and prognosis of this disease in dogs*.

GL Robertson: Physiology of ADH secretion. *Kidney Int*. **21**, 1987, S20, *An in-depth review and excellent overview of the physiology of ADH secretion, beyond what is found in the typical textbook.*

JM Sands, DG Bichet: Nephrogenic diabetes insipidus. *Ann Intern Med*. **144**, 2006, 186, *An interesting review of NDI in humans, with many aspects that are relevant to the advanced critical care veterinary practice*.

* See the CD-ROM for a complete list of references

71 Chapter 71 Syndrome of Inappropriate Antidiuretic Hormone

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71.1 KEY POINTS

- Hyponatremia is the cardinal finding of the symptomatic syndrome of inappropriate antidiuretic hormone (SIADH).
- SIADH can be caused by cerebral disorders, pulmonary disease, or adverse effects of medications. Idiopathic causes have been reported in dogs.
- Hyponatremia of SIADH is characterized by hypoosmolality and inappropriately concentrated urine and urine sodium excretion.
- Renal, adrenal, and thyroid functions are normal, and neither edema, dehydration, nor azotemia is present in animals with SIADH.

71.2 INTRODUCTION

One of the most frequent electrolyte abnormalities in veterinary patients is hyponatremia. Most cases are temporary and without symptoms. One cause of hyponatremia that may be associated with symptoms and can be fatal is Syndrome of inappropriate antidiuretic hormone (SIADH).

Antidiuretic hormone (ADH) deficiency is relatively well known and is referred to as *central diabetes insipidus*. The antithesis of diabetes insipidus, an excess of ADH remains an obscure rarity in animals based on the frequency of case reports,[1-6] but its true incidence may be more common than diabetes insipidus. SIADH, also called *Schwartz-Bartter syndrome,* is characterized clinically in people by symptoms of depression and confusion. Affected animals may have central nervous system disease, pulmonary disease, or conditions requiring drugs that can cause SIADH.

The failure to recognize the true incidence of SIADH may be caused by lack of clinical suspicion, transient nature of some forms of SIADH, insufficient monitoring, rapid demise of the patient, or clinician distraction from investigating and managing concurrent diseases. Recognition of SIADH is important for many reasons, including causes that can be iatrogenic and remedied by drug withdrawal, or patient death that can be iatrogenic if SIADH is managed too aggressively.

71.3 CAUSES

ADH, also known as vasopressin, normally is secreted in response to an increase in serum osmolality (serum sodium concentration) or to maintain normal blood pressure and intravascular volume (see Chapter 177, Vasopressin). ADH actions are achieved by the promotion of free water resorption by the kidneys. Serum osmolality is monitored by the anterior portion of the hypothalamus. If blood pressure is normal or elevated, ADH secretion normally is inhibited by pressure receptors in the atria and great veins. A rise in serum osmolality is a more sensitive monitor (1% rise) and typical stimulus for ADH secretion than a decrease in blood pressure (9% decrease).[7,8] SIADH is defined as an excess of ADH without hypovolemia or hyperosmolality.

SIADH can be caused by cerebral disorders, pulmonary disease, or adverse effects of medications (Box 71-1).[7] The cause in some cases remains idiopathic. Three cases of idiopathic SIADH have been reported in dogs.[2,3] Cerebral causes of SIADH in humans include hypothalamic tumors, head trauma, meningitis, encephalitis, cerebrovascular accidents, and hydrocephalus. Hypothalamic tumors, granulomatous meningoencephalitis, and probable distemper encephalitis have been reported to cause SIADH in dogs.[5,6] Intracranial disease may directly stimulate the supraoptic or paraventricular nuclei to secrete ADH or may alter the osmoreceptors to inappropriately stimulate ADH secretion. Other cerebral causes of SIADH are perception of nausea, pain, and psychologic stress.[7]

Pulmonary diseases causing SIADH include tumors that ectopically produce ADH or diseases that interrupt the inhibitory impulses in vagal afferents from stretch receptors in the atria and great veins. Examples in humans have included tuberculosis pneumonia, aspergillosis, and lung abscesses. A dog had SIADH associated putatively with dirofilariasis.[1] Rarely, SIADH in humans has been caused by malignant tumors outside the thorax that have ectopically produced ADH.[7] In addition, positive-pressure ventilation may inhibit low-pressure baroreceptors and stimulate the release of ADH.

71.3.1 Box 71-1 Some Causes of the Syndrome of Inappropriate Secretion of ADH[7]

71.3.1.1 Central Nervous System Disorders

- Head trauma
- Hydrocephalus
- Cerebrovascular accidents
- Brain tumor
- Meningitis
- Encephalitis

71.3.1.2 Pulmonary Lesions

- Bacterial pneumonia
- Aspergillosis
- Lung tumors
- Positive-pressure ventilation

- Dirofilariasis

71.3.1.3 Malignancies

- Pancreatic carcinoma
- Prostatic carcinoma
- Thymoma
- Osteosarcoma

71.3.1.4 Drugs

- Antidepressants
- Neuroleptics
- Antineoplastics
- Nonsteroidal antiinflammatory drugs
- Opioids

71.3.1.5 Others

- Pain
- Nausea
- Psychological stress

ADH, Antidiuretic hormone.

Drugs may either increase ADH secretion or potentiate its action.[7,8] Drugs that are known to increase ADH secretion in humans include antidepressants (especially tricyclic antidepressants and monoamine oxidase inhibitors), anticancer drugs (intravenous cyclophosphamide and vinca alkaloids), opioids, and neuroleptics. Drugs that potentiate ADH action include cyclophosphamide and nonsteroidal antiinflammatory drugs.

The thirst center in the hypothalamus monitors plasma osmolality and extracellular fluid volume. If the patient is conscious, psychologically normal, and has a normal thirst center, water intake will subside to compensate for the reduction in plasma osmolality and expanded extracellular fluid volume of SIADH.[8] Patients receiving fluid therapy, under sedation or anesthesia, that are psychologically deranged, or with CNS disease affecting the thirst center have impaired ability to compensate for SIADH.

71.4 CLINICAL SIGNS

The clinical signs found in patients with SIADH depend on the cause of the syndrome and on the serum sodium concentration. Signs of a CNS disease, pulmonary disorder, surgical or traumatic stress, or drug intoxication may overshadow signs of SIADH. This may account, in part, for its rare recognition in companion animals. Regardless of its cause, if the serum sodium is severely decreased (less than 120 mEq/L), signs of hyponatremia may prevail. These include nausea, anorexia, vomiting, irritable behavior, confusion, head pressing, seizures, cardiac arrhythmias, and coma. Neither hypertension nor edema will be present.

71.5 LABORATORY FINDINGS

The outstanding initial abnormal laboratory finding in patients with clinical manifestations of SIADH is hyponatremia secondary to renal retention of free water and ongoing urinary sodium losses. Sodium is lost in the urine despite hyponatremia, because the secretion of renin and aldosterone is inhibited by normovolemia with expanding extracellular fluid caused by water retention. Serum osmolality will be less than 280 mOsm/kg, urine osmolality will be more than 150 mOsm/kg; urine sodium values are usually more than 20 mEq/L. Atrial natriuretic peptide is secreted in response to expanding extracellular fluid volume, which further inhibits renin and aldosterone and promotes natriuresis. Even though water is retained, edema usually does not develop because of continuing natriuresis. The degree of natriuresis is quite variable and is dependent on the quantity of dietary sodium.[7]

Other serum constituent concentrations, such as potassium and chloride, may also be diluted. Hypochloridemia may be severe enough to cause metabolic alkalosis. Blood urea nitrogen and uric acid concentrations are decreased by dilution and increased glomerular clearance.[7] An increased blood urea nitrogen concentration excludes a diagnosis of SIADH.

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71.6 DIAGNOSTIC IMAGING FINDINGS

If non–drug-induced SIADH is suspected, evidence for possible intrathoracic or intracranial lesions should be sought by routine radiographs and, in some cases, computed tomography or magnetic resonance imaging.

71.7 DIAGNOSIS

A clinical diagnosis can be based on finding the characteristic clinical features of SIADH and the exclusion of other causes of hyponatremia. Plasma ADH determination is unnecessary for diagnosis. The water loading test can aggravate water intoxication of SIADH and is unnecessarily hazardous.

The clinical features of SIADH are most easily confused with those of primary hypoadrenocorticism. It differs from primary hypoadrenocorticism in having normal to low levels of blood urea nitrogen and serum potassium concentrations. Primary hypoadrenocorticism is associated with azotemia and hyperkalemia. Other differential diagnoses for hyponatremia include congestive heart failure, nephrosis, severe liver disease, hyperglycemia, and hyperlipidemia. In SIADH without unrelated disease, renal, adrenal, cardiac, and liver functions are normal, and blood glucose concentration is normal.

71.8 TREATMENT

Whenever possible, the cause for SIADH should be determined and corrected. The treatment of choice is discontinued fluid administration and restricted access to water. However, this may be insufficient in severe cases.

In acute severe cases, emergency treatment may include hypertonic (3%) saline, which should be given slowly in an intravenous dose over 2 to 4 hours if neurologic signs are thought to be secondary to acute hyponatremia and resulting cerebral edema. Isotonic saline infusion is unsuitable because of its low concentration of sodium, which will be excreted in the urine while the water will be retained, worsening the hyponatremia. When hyponatremia may have been present for more than 48 hours, care must be taken to prevent central pontine myelinolysis (osmotically induced demyelination).[9] Serum sodium should not increase with treatment by more than 12 mEq/L q24h. The initial goal should be to increase serum sodium concentration to 125 to 130 mEq/L in a carefully controlled manner. When hypertonic saline is used, furosemide may also be beneficial to inhibit reabsorption of water in the renal tubules to reduce the risk of volume overload. Sodium and potassium should be supplemented as needed.

A tetracycline, demeclocycline, inhibits the action of ADH on the renal tubules. It has been effective in treating humans with SIADH caused by excessive secretion from hypothalamic nuclei or by the secretion of ectopic ADH. However, it is potentially nephrotoxic and renal function must be monitored closely. Improvement from demeclocycline treatment may take 1 to 2 weeks. A safe and effective dosage of demeclocycline in dogs has not been established. Lithium will also inhibit the action of ADH on the renal tubules, but its use is precluded by its toxicity, which is greater than that of demeclocycline.

71.9 PROGNOSIS

The prognosis for patients with SIADH depends on the cause. If caused by infection or drugs, withdrawal of the drug and successful treatment of the infection will lead to a cure. If secondary to a malignant tumor that cannot be excised completely or destroyed by radiation, SIADH usually is incurable but can be controlled with water restriction and sodium supplementation.

71.10 SUGGESTED FURTHER READINGast;

WJ Biewenga, A Rijnberk, JA Mol: Inappropriate vasopressin secretion in dogs. *Tijdschr Diergeneeskd*. **113**, 1988, 104, *Description of a dog with idiopathic SIADH*.

PJ Brofman, KAB Knostman, SP DiBartola: Granulomatous amebic meningoencephalitis causing the syndrome of inappropriate secretion of antidiuretic hormone in a dog. *J Vet Intern Med*. **17**, 2003, 230, *Description of a young dog with amebic meningoencephalitis that developed SIADH. First reported cases of encephalitis or meningitis causing SIADH in dogs*.

DM Houston, DG Allen, SA Kruth, et al.: Syndrome of inappropriate antidiuretic hormone secretion in a dog. *Can Vet J*. **30**, 1989, 423, *Description of a 4-year-old dog with a meningeal sarcoma in the region of the dorsal hypothalamus and SIADH*.

DP O'Brien, RA Kroll, GC Johnson, et al.: Myelinolysis after correction of hyponatremia in two dogs. *J Vet Intern Med*. **8**, 1994, 40, *Case report of two dogs, the first describing delayed neurologic deterioration from* *central myelinolysis in dogs after rapid correction of severe hyponatremia (<110 mEq/L). Excellent description of clinical signs, magnetic resonance images, postmortem findings, and review of the literature.*

A Rijnberk, WJ Biewenga, JA Mol: Inappropriate vasopressin secretion in two dogs. *Acta Endocrinol.* **117**, 1988, 59, *Report of two dogs with idiopathic SIADH.*

* See the CD-ROM for a complete list of references

72 Chapter 72 Thyroid Storm

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72.1 KEY POINTS

- Thyroid storm is a newly described syndrome of acute thyrotoxicosis in veterinary patients that occurs primarily in hyperthyroid cats.
- The pathogenesis is unknown but probably results from rapid increases in serum thyroid hormone levels coupled with activation of the sympathetic nervous system.
- An event often triggers thyroid storm, although the event may not be readily apparent.
- Clinical signs may include hyperthermia, central nervous system disturbances, acute or severe vomiting and diarrhea, abdominal pain, icterus, cardiac murmurs with or without arrhythmias, pleural effusion, pulmonary edema, tachypnea, hypertension, retinopathies, extreme muscle weakness and cervical ventroflexion, thromboembolic disease, and sudden death.
- Diagnosis is based on clinical signs and evidence of elevated serum thyroid hormones.
- Treatment is aimed at reducing production and secretion of thyroid hormones, blocking peripheral actions of thyroid hormones, systemic support, and elimination of the precipitating event.
- Successful outcome depends on rapid recognition of the clinical syndrome and aggressive therapy.

72.2 INTRODUCTION

Thyroid storm is a syndrome described in human medicine to define a multisystem disorder resulting from organ exposure to excessive amounts of thyroid hormone. This form of acute thyrotoxicosis can be life threatening and is a significant cause of mortality in human emergency rooms. Thyrotoxicosis describes any condition in which there is an excessive amount of circulating thyroid hormone, whether from excess production and secretion from an overactive thyroid gland, leakage from a damaged thyroid gland, or from an exogenous source. In contrast, hyperthyroidism describes thyroid gland hyperfunction. Therefore acute thyrotoxicosis may occur in the absence of thyroid gland hyperfunction, although this is rare in veterinary medicine.

In humans, thyroid storm can occur at any age. It can be present in euthyroid patients as well as treated and partially treated hyperthyroid patients. Although this is a well-recognized syndrome in human medicine, it has not been described as a clinical entity in veterinary medicine. Hyperthyroidism is common in older feline patients. It is also seen rarely in dogs with thyroid carcinoma or extreme oversupplementation of thyroid replacement hormone in hypothyroid dogs. Hyperthyroid cats that experience an acute exacerbation of thyrotoxicosis may be said to have thyroid storm. This chapter will discuss the human syndrome and define a similar syndrome in hyperthyroid veterinary patients. The clinical signs of and treatment modalities for feline patients suffering from thyroid storm will also be presented.

72.3 PATHOGENESIS

Although the exact pathogenesis of thyroid storm remains to be elucidated, several factors appear to be involved, including high levels of circulating thyroid hormones, rapid increases in circulating thyroid hormones, hyperactivity of the sympathetic nervous system, and an increased cellular response to thyroid hormone.

72.3.1 High Levels of Circulating Thyroid Hormones

Although one would expect circulating thyroid hormones to be increased in patients with thyroid storm, in human medicine there is no difference between serum thyroid hormone levels in these patients and in more stable hyperthyroid patients. The diagnosis is therefore made primarily based on clinical signs.[1]

72.3.2 Rapid, Acute Increases in Circulating Thyroid Hormones

The magnitude of change in the serum thyroid hormone levels may be more important than the actual levels themselves. This would explain the occurrence of thyroid storm following radioactive iodine therapy and thyroid surgery that damage the thyroid gland and cause release of hormone or following abrupt cessation of antithyroid medication resulting in the rapid rise of serum thyroid hormone levels.[2] Certainly, nonthyroidal illness, known to be a precipitating factor in human medicine, has been shown to alter binding of thyroid hormones to their carriers and could be responsible for rapid alteration of circulating thyroid hormone as well.

72.3.3 Hyperactivity of the Sympathetic Nervous System

Activation of the sympathetic nervous system has been implicated in the onset of thyroid storm.[3] Many of the clinical signs and physiologic signs are similar to those seen during catecholamine excess. Serum and urine catecholamine levels in humans are within normal limits during thyroid storm. However, thyroid hormones can alter tissue sensitivity to catecholamines at the cell surface receptor as well as the intracellular signaling levels, and this increased sensitivity may result in the clinical signs seen during thyroid storm. In addition, many of these clinical signs are controlled by β-adrenergic blockade.

72.3.3.1 Box 72-1 Potential Precipitating Events for Feline Thyroid Storm

- Radioactive iodine therapy
- Thyroidal or parathyroidal surgery
- Abrupt withdrawal of antithyroid medications
- Stress
- Nonthyroidal illness
- Administration of iodinated contrast dyes
- Administration of stable iodine compounds

- Vigorous palpation of the thyroid

72.3.4 Increased Cellular Response to Thyroid Hormones

This effect has been implicated in the cause of thyroid storm resulting from infection, sepsis, hypoxemia, hypovolemia, and lactic acidosis or ketoacidosis.[4]

72.4 PRECIPITATING EVENTS

In most cases of thyroid storm in humans, a precipitating event can be identified, although no known cause is found in up to 2% of cases.[5] The most common precipitating events are infection, thyroidal and nonthyroidal surgery, radioactive iodine therapy, administration of iodinated contrast dyes, administration of stable iodine, withdrawal of antithyroid medication, amiodarone therapy, ingestion of excessive amounts of exogenous thyroid hormone, vigorous palpation of the thyroid gland, severe emotional stress, and a variety of acute nonthyroidal illnesses. Common events that may precipitate thyroid storm in feline hyperthyroid patients may include radioactive iodine therapy, abrupt withdrawal of antithyroid medication, thyroid surgery, vigorous thyroid palpation, stress, administration of stable iodine compounds, as well as any of the other precipitating factors found in humans (Box 72-1).

72.5 CLINICAL SIGNS

Thyroid storm is the acute exacerbation of clinical signs of thyrotoxicosis; however, the diagnosis of thyroid storm in human medicine is based on the prevalence of four major clinical signs. These include (1) fever, (2) central nervous system (CNS) effects from mild agitation to seizures or coma, (3) gastrointestinal (GI) and hepatic dysfunction ranging from vomiting, diarrhea, and abdominal pain to unexplained jaundice, and (4) cardiovascular effects including sinus tachycardia, atrial fibrillation, ventricular tachycardia and congestive heart failure. The combination of these clinical signs along with identification of a precipitating event allows for the diagnosis of thyroid storm.[5] In cats with presumed thyroid storm, many of these clinical signs also occur (Box 72-2).

Auscultation may reveal a cardiac murmur or arrhythmia (most often a gallop rhythm). Inspiratory crackles or dullness in the lung fields may be heard if pulmonary edema or pleural effusion is present, respectively.[6] Mild to severe hypertension may also be present during thyroid storm in cats.[7] Retinopathies, including hemorrhage, edema, degeneration, or even retinal detachment may be found, especially in hypertensive thyrotoxic cats.[8] Tachypnea and hyperthermia may be present, and absent limb motor function may be detected as a result of thromboembolic disease occurring from acute thyrotoxicosis.[9] Sudden death may also occur. Severe, acute muscle weakness and ventroflexion of the neck may be seen in acutely thyrotoxic cats, often associated with hypokalemia.

72.5.1 Box 72-2 Clinical Signs Associated With Feline Thyroid Storm

72.5.1.1 Constitutional Signs

Hyperthermia

Dehydration

72.5.1.2 Cardiovascular Signs

Arrhythmias

Atrial fibrillation, ventricular tachycardia

Gallop rhythm

Sinus tachycardia

Congestive heart failure

Cardiomegaly

Pleural effusion

Pulmonary edema

Hypertension

Thromboembolic disease

72.5.1.3 Respiratory Signs

Tachypnea

72.5.1.4 Neuromuscular Signs

Behavior changes

Seizures

Muscle weakness

Cervical ventroflexion

72.5.1.5 Gastrointestinal and Hepatic Signs

- Abdominal discomfort or pain
- Vomiting
- Diarrhea
- Icterus

72.5.1.6 Ocular Signs

- Hyphema
- Retinal lesions
- Retinal detachment

72.6 DIAGNOSIS

The diagnosis of thyroid storm is based on identification of thyrotoxicosis, clinical signs, and evidence of a precipitating event.[5] Thyrotoxicosis in hyperthyroid cats is demonstrated by an elevated total T_4 level, or a total T_4 level in the high-normal range combined with an elevated free T_4 level. The total T_4 level may be in the normal range in a hyperthyroid cat, but it is expected that in cases of thyroid storm, the total T_4 and free T_4 levels will be above the normal range. In human medicine, thyroid storm is diagnosed based on a point system assigned to each of the main clinical components: fever, CNS signs, GI signs, and cardiovascular signs, as well as presence or absence of a precipitating event.[5] In hyperthyroid feline patients, thyroid storm may be diagnosed based on clinical 308
signs of acute thyrotoxicosis. In some cases a precipitating event may be identified. 309

72.7 LABORATORY ABNORMALITIES

Laboratory abnormalities result from uncomplicated thyrotoxicosis[10]; there is no distinguishing laboratory value for feline thyroid storm. In the hyperthyroid cat, hematologic abnormalities may include a mild erythrocytosis, macrocytosis, and Heinz body formation. In humans with thyroid storm, a leukocytosis with left shift in the absence of active infection or inflammation has been identified.[11] In hyperthyroid cats a mature neutrophilia, lymphopenia, and eosinopenia are more commonly identified as a stress response. Biochemical abnormalities seen in people with thyroid storm include a mild hyperglycemia and hypercalcemia. Elevated liver enzyme values are often seen as well, and hyperbilirubinemia may occur in severe cases; this finding carries a poor prognosis. In hyperthyroid cats, elevated liver enzyme levels, a mild hyperglycemia, and severe hypokalemia may be seen in patients with acute thyrotoxicosis. A decreased sodium-to-potassium ratio may be seen in thyrotoxic cats who experience heart failure with pleural effusion.[12] Radiographs may reveal cardiomegaly and/or evidence of congestive heart failure.

72.7.1 Treatment

Treatment of thyroid storm is aimed at controlling the four major problematic areas: (1) to reduce the production and/or secretion of thyroid hormones, (2) to counteract the peripheral effects of thyroid hormones, (3) to provide systemic support, and (4) to identify and eliminate the precipitating factor.[13]

72.7.1.1 Reduction in the Production or Secretion of New Thyroid Hormones

The thioimidazole compound methimazole inhibits iodine incorporation into tyrosyl residues of thyroglobulin and thus prevents the synthesis of active thyroid hormone. In this way, methimazole should be the first line of defense against thyroid storm. However, it does not prevent the secretion of already formed thyroid hormones. Methimazole may be given orally, transdermally, or even rectally in cats. The dosage should be at the high end in cats that have normal renal function (5 mg per cat PO q12h). If there is suspected renal insufficiency or failure, the dosage of methimazole should be reduced by half to prevent a rapid decrease in renal blood flow.

Methimazole will block the formation of new, active thyroid hormone, but other measures must be instituted to prevent further secretion of formed hormone, which is stored in high concentrations in the thyroid gland. This can be done with stable iodine compounds such as potassium iodide. These compounds, in large dosages, can also decrease the synthesis rate of thyroid hormone. They must be given 1 hour after methimazole administration, because a large load of iodine will initially stimulate thyroid hormone production. Potassium iodide may be given at 25 mg PO q8h. Instead of potassium iodide, lipid-soluble radiographic contrast agents, such as iopanoic acid, may be given at 100 mg per cat q12h. Although iopanoic acid is available in parenteral form, oral administration is safer because it is a very hyperosmolar agent. This compound has the additional advantages of blocking peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3), blocking T_3 from binding to its receptor, and inhibiting thyroid hormone synthesis.

72.7.1.2 Inhibition of Peripheral Effects of Thyroid Hormone

The most rapid relief of signs caused by thyroid storm is accomplished with medications that block the β-adrenergic receptors, such as propranolol and atenolol. Propranolol, a nonselective β-adrenergic blocker, is used most commonly as a sympatholytic agent in human medicine, but it is inherently difficult to use in cats because of its poor oral bioavailability and short half-life, requiring administration every 8 hours in this species. The use of propranolol has been largely superseded by atenolol because of its selectivity and once-daily administration. However, propranolol inhibits the peripheral conversion of T_4 to T_3, although this effect happens slowly.[14] Therefore propranolol may be advantageous in severely thyrotoxic cats. High-end dosages of propranolol should be used to ensure β-adrenergic blockade at 5 mg PO q8h or 0.02 mg/kg IV over 1 minute. Alternatively, atenolol, a selective β_1-adrenergic blocker that has better oral bioavailability, may be used at 1 mg/kg q12-24h. In emergent situations, the short-acting β_1-blocker esmolol constant rate infusion [CRI] may be used intravenously at a loading dose of 0.1 to 0.5 mg/kg over 1 minute, followed by a CRI of 10 to 200 μg/kg/min (see Chapters 190 and 191, Antiarrhythmic Agents and β-Blockers, respectively).

An extreme method to counteract the peripheral actions of excess thyroid hormones is to reduce the systemic levels that are already present. Peritoneal dialysis, plasmapheresis, and hemodialysis have been used in human medicine, as has cholestyramine, which binds to thyroid hormone in the GI tract, and inhibits enterohepatic circulation. These methods rarely are used in human patients and probably have limited use in veterinary patients with thyroid storm.

72.7.1.3 Systemic Support

The third arm of treatment for thyroid storm involves reversing the effects of thyroid hormones on the body. Hyperthermia should be treated with judicious use of parenteral fluids and fans. Volume depletion is another common systemic effect of thyroid storm and this should be treated with intravenous isotonic crystalloid fluid replacement. Colloid fluid therapy is generally not indicated unless severe GI disease or another syndrome resulting in low oncotic pressure is present. Potassium supplementation should be added as necessary (some patients with thyroid storm become acutely hypokalemic). Dextrose supplementation of 5% to 10% should be considered, if needed, and B vitamin supplementation may prevent thiamine deficiency in hyperthyroid cats.

Cardiac disturbances are common in humans with thyroid storm, and it is not uncommon for cats with thyroid storm to arrive in cardiac failure. β-Adrenergic blockade therapy, as described earlier, may be also be helpful for managing cardiac failure because of its effects in reducing the elevated heart rate caused by thyrotoxicosis. Furosemide (1 to 4 mg/kg IV or IM q1-6h as needed; 0.5 to 2 mg/kg PO q6-24h), angiotensin-converting enzyme inhibitors (enalapril or benazepril at 0.5 to 2 mg/kg PO q12h), isosorbide dinitrate (0.5 to 2 mg/kg PO q8-12h), nitroglycerin (0.25 to 1.5 inch q6-12h topically), or hydralazine (0.5 to 1 mg/kg IV; 0.5 to 2 mg/kg PO, SC, or IV q8-12h) may be useful to manage feline heart failure, but must be used with care in patients with renal compromise (see Chapters 178, 179, and 180, Antihypertensives, Nitroglycerin, and Diuretics, respectively). In all cases, medications should be started at the lowest dosages and titrated upward to effect with close blood pressure monitoring.

Supraventricular arrhythmias are common in humans with thyroid storm, with the most common disturbance being atrial fibrillation. Atrial fibrillation or ventricular tachycardias can also occur in thyrotoxic feline patients. β-Adrenergic receptor blockade as described above is a first-line defense in treating these arrhythmias. A possible sequela in feline patients with heart failure or atrial fibrillation is thromboembolic disease. Anticoagulation should be considered using low-dose aspirin (5 mg/cat q72h), heparin (200 to 400 U/kg SC q6-8h until activated partial thromboplastin time is 1.5 to 2 times prolonged) and low-molecular-weight heparin (100 U/kg SC q6h).

Hypertension is often a complication of thyroid storm in cats. Blood pressure should be checked and antihypertensive therapy instituted as appropriate to include β-blockade as discussed previously or amlodipine (0.625 to 1.25 mg PO or rectally q12-24h). In acute cases of hypertension, nitroprusside may be used as an intravenous CRI at 0.5 to 5 μg/kg/min or nicardipine at 0.5 to 5 mg/kg/min.

In humans with thyroid storm, a relative adrenal insufficiency may occur secondary to increased cortisol clearance. This prompts the administration of glucocorticoids. Studies have not been done in feline patients, and glucocorticoid therapy in patients with thyroid storm remains controversial.

72.7.1.4 Eradication of the Precipitating Factor

In human patients with thyroid storm, a precipitating factor is one of the criteria that define the disease. Precipitating factors should also be investigated thoroughly in cats with thyroid storm. A full workup, including full hematology studies, biochemical analysis, urinalysis, retroviral testing, blood pressure measurement, and imaging studies should be performed. Abnormal findings should be further examined by culturing potentially infected fluids, detailed imaging studies, endoscopy, or other specialized testing. If another abnormality is identified, it should be treated in order to prevent recurrence of thyroid storm.

72.7.2 Outcome

Although thyroid storm is an uncommon finding in human emergency rooms, the mortality rate in patients with this syndrome is significant. Rapid recognition of the problem and aggressive treatment are necessary for a successful outcome. Thyroid storm is not as well defined in feline medicine, although acute manifestations of thyrotoxicosis result in a syndrome that can be considered a feline thyroid storm. Veterinary recognition of this syndrome may be lacking, so it is unknown what the true incidence and mortality from thyroid storm may be in cats. However, it is certainly recognized that death may arise from untreated, acute thyrotoxicosis. As in humans, it is anticipated that early recognition and aggressive treatment of feline thyroid storm will improve veterinary patient survival.

72.8 SUGGESTED FURTHER READING*

HB Burch, L Wartofsky: Life-threatening thyrotoxicosis: thyroid storm. *Endocrinol Metab Clin North Am*. **22**, 1993, 263, *A defining work on thyroid storm syndrome and illustration of the point system used to diagnose this disease in people*.

DL Geffner, JM Hershman: Beta-adrenergic blockade for the treatment of hyperthyroidism. *Am J Med*. **93**, 1992, 61, *A review of the success of β-blocker therapy in people with hyperthyroidism: how it works and what works best*.

RD Kienle, D Bruyette, PD Pion: Effects of thyroid hormone and thyroid dysfunction on the cardiovascular system. *Vet Clin North Am Small Anim Pract*. **24**, 1994, 495, *A good review of the effects of thyroid hormone on the cardiovascular system in veterinary patients*.

CT Mooney: Hyperthyroidism. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, St. Louis, *The chapter in the bible of veterinary internal medicine describing feline and canine hyperthyroidism: pathogenesis, clinical signs, laboratory abnormalities, and treatment modalities*.

ST Tietgens, MC Leinung: Thyroid storm. *Med Clin North Am*. **79**, 1995, 169, *An excellent summary of the syndrome of thyroid storm in human medicine*.

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* See the CD-ROM for a complete list of references

73 Chapter 73 Myxedema Coma

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73.1 KEY POINTS

- Myxedema coma is a misnomer. Many patients in a hypothyroid crisis are not comatose and do not have myxedema.
- Myxedema coma is difficult to diagnose, because it is rare and the clinical and clinicopathologic abnormalities may be nonspecific.
- Rottweiler dogs are at increased risk for a hypothyroid crisis.
- Concurrent disease, most commonly infection (pneumonia), may increase the risk for a hypothyroid crisis. Treatment with steroids, nonsteroidal medication, or surgery may also increase the risk for a hypothyroid crisis.
- Myxedema, obesity, mental dullness, hypercholesterolemia, and nonregenerative anemia are observed in many, but not all, dogs in a hypothyroid crisis.
- Intravenous (IV) administration of levothyroxine at a dosage of 5 μg/kg q12h is a safe and effective treatment for dogs in a hypothyroid crisis.
- Subjective improvement in mentation or ambulation occurs within 24 to 30 hours of IV levothyroxine administration in most dogs.
- When treated appropriately with supportive care and IV levothyroxine, most dogs with myxedema coma respond well and are discharged from the hospital.

73.2 INTRODUCTION

Canine myxedema coma is a rare, life-threatening complication of hypothyroidism.[1-7] In human beings the name *myxedema coma* is considered a misnomer, because human patients with this condition are rarely comatose and do not usually have myxedema.[8,9] Diagnosis of myxedema coma is difficult because it is rare, and therefore little is known of the condition.[1] Diagnosis is further complicated by nonspecific clinical signs. Recognition of an acute hypothyroid crisis in dogs that do not have coma or myxedema may advance the understanding and improve the outcome of dogs with suspected myxedema coma.[1]

73.3 PATHOPHYSIOLOGY

The pathophysiology of myxedema coma is incompletely understood. Thyroid hormones regulate cell function in many organs by binding intranuclear receptors and promoting expression of various enzymes.[10] Thyroid hormones exert chronotropic and inotropic effects in the heart, as well as catabolic, metabolic, calorigenic, and developmental effects in other organs.[10] Therefore decreased thyroid hormone function has a profound effect on many body systems. The clinical hallmarks of myxedema coma in human beings are altered mental status, inadequate thermoregulation, decreased respiratory and cardiovascular function, and concurrent disease.[9,11]

In human beings, altered mental status may be limited to disorientation, confusion, or lethargy.[9] Coma is unusual.[8,9] In dogs, clinical signs such as disorientation and confusion may be difficult to appreciate. Although most dogs in a hypothyroid crisis have mental dullness, coma upon initial examination is uncommon.[1,2,4-6] The pathophysiology of altered mental status is multifactorial and may be a result of decreased blood flow to the brain, hyponatremia, or lack of a direct effect of thyroid hormone on the brain.[9]

The pathophysiology of altered thermoregulation resulting in hypothermia is likely also multifactorial. Inadequate thyroid hormone function in the hypothalamus may result in inability to regulate body temperature.[9] Additionally, a decrease in the calorigenic effect of thyroid hormones contributes to hypothermia.[9] The body temperature of some individuals with myxedema coma may appear to be normal because of a concurrent infection and a fever.[9]

Hypoventilation develops secondary to decreased respiratory system responsiveness to hypoxia and hypercapnia, and may be complicated by obese body condition, muscle weakness, pneumonia, pericardial or pleural effusion, and ascites.[11] In the heart, thyroid hormones increase the number of β-adrenergic receptors and their affinity to catecholamines, thereby increasing the inotropic and chronotropic effects of catecholamines.[10] Hypothyroid cardiomyopathy is also caused by an increase in α-myosin heavy chains (MHC), which have decreased adenosine triphosphatase (ATPase) activity, and a decrease in β-MHCs, which have more adenosine triphosphatase activity.[10] These changes result in hypothyroid cardiomyopathy typified by impaired left ventricular function or atrial fibrillation.[12,13] During a hypothyroid crisis, cardiovascular dysfunction is characterized by bradycardia, decreased cardiac contractility, cardiac enlargement, and hypotension, although diastolic hypertension has also been documented.[11]

Concurrent disease may prevent normal compensatory mechanisms from responding appropriately to a hypothyroid crisis, and may therefore be involved in the pathophysiology of myxedema coma.[9] Absence of concurrent disease in most cases of hypothyroidism may explain why myxedema coma remains rare.

When myxedema does occur, it is thought to develop secondary to accumulation of the glycosaminoglycan hyaluronic acid in the dermis.[6,14] Impaired renal perfusion secondary to decreased cardiovascular function results in inability to excrete water and contributes to development of edema.[11] Excessive secretion of antidiuretic hormone may also contribute to fluid retention and edema in some patients.[15]

73.4 RISK FACTORS

Rottweiler dogs are at increased risk for myxedema coma.[1] Most dogs with myxedema coma are of middle age (median 6 years, range 4 to 10 years).[1] The age of dogs with myxedema coma is not significantly different from the age of other hypothyroid dogs. Female dogs do not appear to be at increased risk compared with other hypothyroid dogs, although myxedema coma is more common in women than in men.[1,8,11] Dogs with untreated hypothyroidism are at increased risk.[1-6]

Most dogs with myxedema coma have a concurrent disorder, most commonly an infection.[1] In a recent report of seven dogs in a hypothyroid crisis, concurrent disease was diagnosed in five.[1] Infection was diagnosed in four of the seven dogs.[1] Three of the four dogs with infection had aspiration pneumonia. Additional infections included foreign body keratoconjunctivitis, pyometra, severe bilateral otitis, and pyoderma.[1] The most commonly observed concurrent infections in humans with myxedema coma are pneumonia, influenza virus, urinary tract infection, and sepsis.[8]

Glucocorticoids were administered to three dogs with myxedema coma within 1 month of a hypothyroid crisis.[1,5] Oral prednisone at a dosage of 0.55 mg/kg q12h lowers the concentration of thyroid hormones in dogs.[16] Nonsteroidal antiinflammatory medications (carprofen and flunixin meglumine) were used in conjunction with glucocorticoids in one dog in a hypothyroid crisis.[1] Nonsteroidal antiinflammatory drugs (NSAIDs) may cause suppression of thyroid stimulating hormone (TSH) secretion.[17] It is therefore possible that administration of glucocorticoids to dogs with untreated hypothyroidism may increase the risk of myxedema coma. An association between NSAIDs, or other thyroid hormone synthesis–altering drugs, and canine myxedema coma may become apparent in the future.

Surgery increases the risk of myxedema coma in human beings and has been reported in three dogs with myxedema coma.[1,6] It is possible that surgery compromises the ability of normal cardiovascular and pulmonary compensatory mechanisms to respond to a hypothyroid crisis, and therefore increases the risk for such a crisis.[8]

Other factors that increase the risk of myxedema coma in human beings include burns, carbon dioxide retention, gastrointestinal hemorrhage, hypoglycemia, infection, hypothermia (most cases are diagnosed during the winter), stroke, trauma, and various medications including anesthetics, barbiturates, β-blockers, diuretics, narcotics, phenothiazines, and tranquilizers.[8]

73.5 CLINICAL SIGNS AND PHYSICAL EXAMINATION FINDINGS

Clinical signs and physical examination findings may be attributed to chronic untreated hypothyroidism, an acute hypothyroid crisis, or concurrent disease. Clinical signs commonly observed in dogs with chronic untreated hypothyroidism include weight gain or obese body condition, lethargy, mental dullness, weakness, and dermatologic abnormalities such as hyperkeratosis, alopecia, or thin hair coat.[7] In a recent study of seven dogs in a hypothyroid crisis, physical abnormalities included overweight or obese body condition (noted in five of seven dogs), nonpitting facial, jaw, or other edema (four of seven), tachypnea (four of seven), alopecia (three of seven), dehydration (two of seven), dermatitis (two of seven), otitis (one of seven), elevated or decreased body temperature (one dog each), heart murmur (one of seven), bradycardia (one dog), or tachycardia (one dog).[1] Neurologic findings included mental dullness (observed in five of seven dogs) and stupor (two of seven). None of the dogs was comatose.[1] In a literature review of five previously published manuscripts describing seven other dogs with myxedema coma, one dog was in a coma on initial examination,[3] although ultimately four of seven dogs developed coma.[2,4-6] Stupor was noted in six of these dogs.[2,4-6]

Most dogs in a hypothyroid crisis do not have all of the classic physical hallmarks including myxedema, hypothermia, bradycardia, hypoventilation, hypotension, and coma.[1,5,6]

73.6 CLINICAL PATHOLOGY

The most common abnormalities noted on complete blood count and serum chemistry screen are a mild nonregenerative anemia, hypercholesterolemia, lipemia, and increased alkaline phosphatase activity.[1] However, not all dogs with severe unregulated hypothyroidism have all of these clinicopathologic abnormalities, and normal cholesterol concentration or hematocrit has been documented in dogs with myxedema coma.[1,5,6] Although hyponatremia and hypoglycemia are well recognized in humans with myxedema coma and have been noted anecdotally in dogs, they were not noted in any of seven dogs in a hypothyroid crisis.[1] Urinalysis and urine culture results are usually normal.[1]

Nonregenerative anemia is associated with hypothyroidism for several reasons. Thyroid hormones bind thyroid hormone receptors on erythroid progenitors and act directly to increase erythroid proliferation.[18] Thyroid hormones also increase expression of the erythropoietin gene, further contributing to red blood cell formation.[18]

The mechanisms by which decreased thyroid hormone function induces dyslipidemia are widely studied and not fully understood. Alterations in both synthesis and transport of lipids are involved in the pathogenesis of hypothyroid dyslipidemia.[19] Decreased messenger ribonucleic acid (mRNA) expression of hepatic low-density lipoprotein (LDL) receptors results in fewer LDL receptors, decreased clearance of LDL by the liver, and elevated plasma LDL concentration.[19] High-density lipoprotein (HDL) subfraction concentration is also altered, with an increase in the subfraction HDL_2, attributed mainly to decreased hepatic lipase activity.[19]

Many possible explanations for hyponatremia have been investigated. These include increased renal reabsorption of sodium, impaired water clearance, increased antidiuretic hormone concentration, low plasma renin activity, and a low aldosterone concentration.[15] Hypoglycemia can develop secondary to reduced insulin clearance or may be observed in patients with concurrent hypoadrenocorticism.[8,20] Sepsis should also be considered in these cases.

Systolic hypotension is reported commonly in humans with myxedema coma, and is thought to develop secondary to bradycardia, decreased cardiac output, and hypovolemia.[8,11] Blood pressure was not measured in most reports of canine myxedema coma.[4-6,14] Systolic hypotension was documented in four of five dogs in which the blood pressure was measured.[1,2] Diastolic hypertension is also recognized in humans with myxedema coma and is believed to develop because of peripheral vasoconstriction and central shunting of blood that occurs as a result of hypothermia and low oxygen consumption.[11]

Hypoxia and hypercarbia are reported in humans with myxedema coma. Venous blood gas analysis has been 312
reported in seven dogs in a hypothyroid crisis.[1,2] Hypercarbia was documented in one of these dogs,[2] and the 313
arterial partial pressure of carbon dioxide ($PaCO_2$)was at the high end of normal in two other dogs[1] and normal in the remaining four dogs.[1] Lactate concentration was increased in five of the six dogs in which it was measured.[1]

Thyroid axis testing is performed to confirm the diagnosis of hypothyroidism. However, results often are not available immediately, and treatment of a hypothyroid crisis must begin before confirmation of a diagnosis. Serum should be stored for future analysis before thyroid hormone supplementation is begun. Severe lipemia can interfere with hormone measurement, further complicating the diagnosis.[1] Hypothyroidism is confirmed based on low thyroxine and high TSH concentrations, although some hypothyroid dogs do not have elevated TSH concentrations. Endogenous TSH concentration was normal in 63% of measurements in dogs with spontaneous hypothyroidism.[21]

73.7 DIFFERENTIAL DIAGNOSIS

Many of the clinical and clinicopathologic abnormalities observed in dogs with myxedema coma are nonspecific. Differential diagnosis for obesity, lethargy, mental dullness, weakness, dermatologic abnormalities, and nonregenerative anemia are discussed elsewhere. Some nonspecific differentials might include chronic inflammatory disease, cardiac disease, metabolic disease (i.e., hypoadrenocorticism), intracranial disease, hypothermia, and sepsis.

Differential diagnoses for edema can be divided into those caused by increased hydrostatic pressure, decreased oncotic pressure, lymphatic obstruction, sodium retention, and vascular endothelial leak syndromes. Such differential diagnoses include heart failure, constrictive pericarditis, ascites, venous obstruction or compression, heat, hormonal imbalance, protein-losing nephropathy or enteropathy, liver disease, malnutrition, neoplasia, renal hypoperfusion, sepsis, and excess secretion of renin, angiotensin, or aldosterone.

Differential diagnoses for hypercholesterolemia includes hypothyroidism, diabetes mellitus, hyperadrenocorticism, protein-losing glomerulopathy, cholestatic disease, postprandial hyperlipidemia, primary hyperlipidemia (Miniature Schnauzers, Shetland Sheepdogs), lipoprotein lipase deficiency (cats), idiopathic causes (Doberman Pinschers, Rottweilers), and iatrogenic causes (glucocorticoids).

73.8 TREATMENT

Treatment is divided into supportive care, thyroid hormone supplementation, and treatment of concurrent conditions. Hypotension can be treated cautiously with fluids and vasopressors (see Chapter 176, Vasoactive Catecholamines).[11] Dogs must be observed carefully for signs of fluid overload, which may exacerbate underlying cardiac disease or dysfunction. Hypothermia is treated by wrapping the dog with blankets and keeping the room warm.[11] Heating pads are avoided because they can lead to vasodilation and worsening hypotension.[11] If respiratory depression is profound, mechanical ventilatory support is needed.[1,2] Hyponatremia can be corrected slowly (no more than 0.5 mEq/hr) with 0.9% saline solution.[11]

Ultimately, clinical signs resolve with thyroid hormone supplementation. Thyroid hormone is usually administered before results of thyroid axis testing are available, and before the diagnosis of a hypothyroid crisis is confirmed. IV levothyroxine has a higher bioavailability than does oral levothyroxine, resulting in a more rapid clinical response. IV levothyroxine at a dosage of 5 µg/kg administered q12h is safe and effective in dogs in a hypothyroid crisis.[1] Adverse side effects of IV thyroid hormone supplementation in humans may be reduced with thyroxine (T_4) rather than with intravenous triiodothyronine (T_3).[22,23] Such adverse side effects include cardiac arrhythmias, angina pectoris, and pneumonia.[23] Mortality of humans with myxedema coma is increased with high dosages of IV levothyroxine (>500 µg/24 hours, which is equivalent to about 7 µg/kg/24 hours).[24] Dogs should be monitored closely for these complications. Administration of IV levothyroxine may have led to the development of pneumonia in two dogs.[1] When the hypothyroid crisis is resolved, the oral route can be used (0.1 mg/5 to 7 kg PO q12h).[7]

Treatment of concurrent disease such as pneumonia, other infections, cardiac disease, concurrent endocrinopathy, or any other illness will facilitate recovery. Discontinuation of any medication that may have exacerbated the hypothyroid crisis is also recommended.

73.9 OUTCOME

Most dogs with myxedema coma respond well to therapy when given IV levothyroxine.[1,3] Seven of eight reported dogs that received IV levothyroxine were discharged from the hospital (87%).[1,3] Subjective improvement in mentation or ambulation occurs within 24 to 30 hours of administration of IV levothyroxine in most dogs.[1] Severity of concurrent disease, persistent hypothermia, advanced age, and degree of mental alteration (coma) is associated with a poor prognosis in humans.[25]

73.10

SUGGESTED FURTHER READING*

E Fliers, WM Wiersinga: Myxedema coma. *Rev Endocr Metab Disord*. **4**, 2003, 137, *A review of myxedema coma in humans that offers some insight on pathophysiology, diagnosis, and treatment.*

WH Pullen, RS Hess: Hypothyroid dogs treated with intravenous levothyroxine. *J Vet Intern Med*. **20**, 2006, 32, *A retrospective study which is the largest, most detailed report of canine myxedema reported to date, bringing to light the need to treat dogs in hypothyroid crisis but do not necessarily have myxedema or coma.*

I Rodriguez, E Fluiters, LF Perez-Mendez, et al.: Factors associated with mortality of patients with myxoedema coma: prospective study in 11 cases treated in a single institution. *J Endocrinol*. **180**, 2004, 347, *A prospective study that found that a coma, the Glasgow score, and the APACHE II score were associated with fatal outcome*.

CR Wall: Myxedema coma: Diagnosis and treatment. *Am Fam Physician*. **62**, 2000, 2485, *A review of myxedema coma in humans that focuses on diagnosis and treatment but not on pathophysiology*.

T Yamamoto, J Fukuyama, A Fujiyoshi: Factors associated with mortality of myxedema coma: report of eight cases and literature survey. *Thyroid*. **9**, 1999, 1167, *A retrospective study of five patients and literature review of 82 additional patients. The authors report that age, high-dosage thyroid hormone supplementation, and cardiac disease are risk factors for fatal outcome of myxedema coma*.

* See the CD-ROM for a complete list of references

74 Chapter 74 Pheochromocytoma

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74.1 KEY POINTS

- Pheochromocytoma is a tumor of the chromaffin cells of the adrenal medulla.
- Clinical signs may include hypertension and manifestations of hypertension, weakness, syncope, lethargy, vomiting, diarrhea, tachypnea, abdominal distention, tachyarrhythmias, and/or abdominal pain.
- Most pheochromocytomas in small animals are diagnosed either by abdominal imaging or during postmortem examination.
- Definitive treatment for a pheochromocytoma is surgical excision.
- Preoperative, perioperative, and postoperative treatment may be challenging.
- With complete surgical resection and an uneventful postoperative course, even dogs with vena caval thrombi may experience a significant survival time, reported from 18 months to 3 years.

74.2 INTRODUCTION

Pheochromocytoma is a tumor of the chromaffin cells of the adrenal medulla. These cells synthesize, store, and secrete catecholamines in response to sympathetic stimulation (Color Plates 74-1 and 74-2).[1] Chromaffin cells are also termed APUD cells, because they are responsible for amine precursor uptake and decarboxylation. Pheochromocytoma may occur alone, or as part of the multiple endocrine neoplasia syndrome. In humans this is a heritable constellation of two or more endocrine neoplasias (or hyperplasia), usually involving the parathyroid and thyroid glands in addition to the adrenal gland.[2] Extraadrenal pheochromocytomas (paragangliomas) occur rarely. Most (48% to 80%) of pheochromocytomas in small animals and 30% to 76% in humans are diagnosed on postmortem examination, or as incidental findings on abdominal ultrasonography, and the patient may be clinically asymptomatic.[1,3-5] It is thought that pheochromocytomas represent between 0.01% and 0.13% of all canine tumors; however, this number may be low, because the tumor may be benign or nonfunctional and thus not suspected.[6] These tumors may be both locally invasive and metastatic.[3,5] Most pheochromocytomas in humans secrete norepinephrine (NE) (versus epinephrine), but this has not been studied in dogs or cats.[2] It is thought that negative feedback of NE on tyrosine hydroxylase (which converts tyrosine to dopa, leading to synthesis of more NE) does not work normally in the tumor cells, or that the tumor metabolizes NE so quickly that the levels required for negative feedback are never reached.[2]

74.3 CLINICAL SIGNS

In dogs with a pheochromocytoma, approximately 30% to 50% have clinical signs attributable to the tumor. Dogs tend to be older (10 to 12 years),[1,5,8] and there is no gender predilection.[7,8] Clinical signs may include hypertension, manifestations of hypertension (e.g., blindness from retinal detachment), weakness, collapse, lethargy, vomiting, diarrhea, tachypnea, abdominal distention, syncope, tachyarrhythmias, and/or abdominal pain.[5,8] These signs may be sustained or paroxysmal. Because the pheochromocytoma is not innervated like a normal adrenal gland, it is unclear what stimuli cause secretion of catecholamines from the tumor. A Budd-Chiari–like syndrome resulting from tumor invasion and extension up the caudal vena cava has been reported in a dog.[9] Approximately 15% to 38% of dogs with a pheochromocytoma have neoplastic invasion of the caudal vena cava; however, clinical signs are not reliably associated with the extent or presence of vena caval invasion.[6,10]

Concurrent pheochromocytoma and hyperadrenocorticism have been reported in six dogs, and some clinical signs (e.g., panting) may overlap.[11] Rupture of pheochromocytomas may result in hemoperitoneum or hemoretroperitoneum.[12,13] Dogs may exhibit neurologic deficits or paraparesis secondary to metastatic tumor in the spinal canal, or secondary to aortic thromboembolic disease.[5,6,8] Cardiac arrhythmias may include third-degree atrioventricular block, supraventricular tachycardia, or ventricular ectopy.

Of the few cats in the literature with an antemortem diagnoses of a pheochromocytoma, clinical signs consisted of lethargy, vomiting, polyuria, polydipsia, or were associated with systemic hypertension (congestive heart failure and retinal detachment).[14-16]

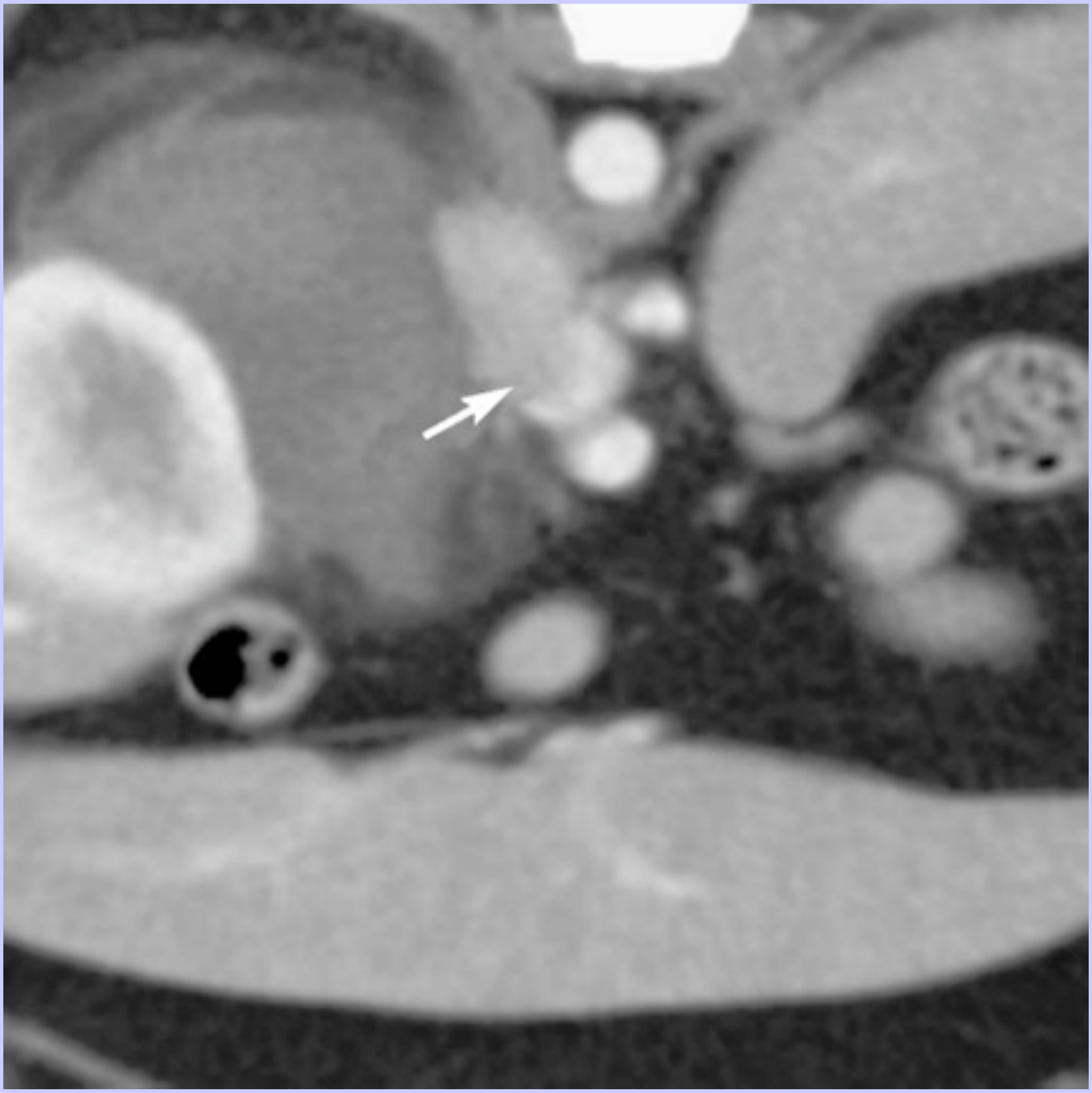
74.4 DIAGNOSIS

As in humans, most pheochromocytomas in small animals are incidental findings, diagnosed by abdominal imaging or postmortem examination. In some dogs, an abdominal mass may be palpated.[5,8]

Abdominal radiography may show mineralization in the area of the adrenal glands, or may demonstrate retroperitoneal effusion or an abdominal mass effect associated with the tumor (30% to 50% of cases).[5,18] Chest radiographs may show cardiomegaly and pulmonary venous congestion or pulmonary edema secondary to chronic hypertension or tachycardia.[1,5] These findings may be confirmed via echocardiography.[7] Rarely, metastatic disease may be seen on thoracic radiographs.[7,8]

Sixty-five to eighty-three percent of pheochromocytomas in dogs are detected via abdominal ultrasonography, making it a useful first-line imaging modality.[2] The origin and architecture of the mass, as well as blood flow within the mass and invasion into adjacent structures, may be determined. Pheochromocytomas seem to have a 314 higher likelihood for 315 vena caval invasion than do adrenocortical tumors,[16] but ultrasonographically they appear similar to adenocarcinomas.[17] It is difficult to determine the cellular origin of an adrenal mass based on ultrasonography, and some masses may be too small for detection by this means.[1,2] Invasive pheochromocytomas have been reported to invade not only the vena cava, but also the aorta, renal veins, and hepatic veins.[10] Ultrasound-guided biopsies may be obtained, if indicated, but caution should be exercised.

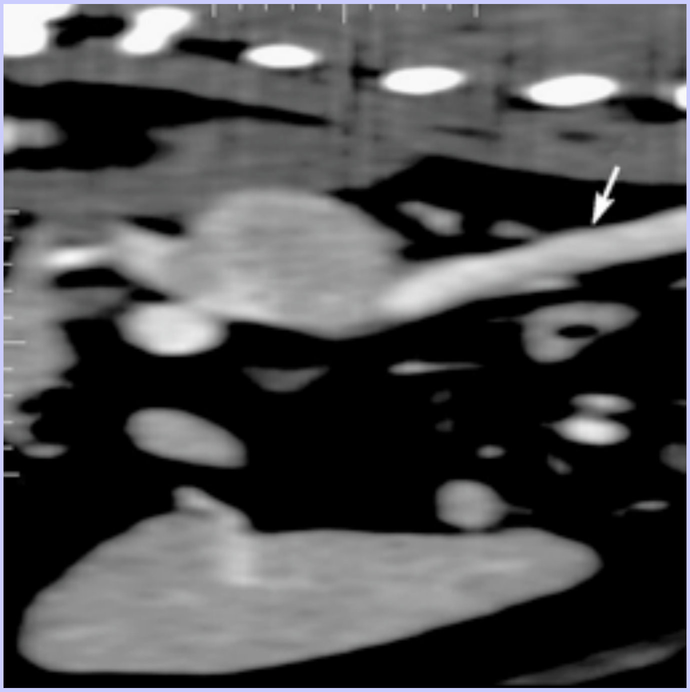
Figure 74-1 Transverse helical postcontrast computed tomography image at the level of the cranial pole of the right kidney. A right adrenal mass is seen, and a large filling defect is present in the caudal vena cava at that level *(arrow)*. This mass was determined to be a pheochromocytoma by histopathology.



Advanced imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) are very helpful for determining the size of the tumor and the extent of tumor invasion, although these require general anesthesia in the veterinary patient. Nonionic, low-osmolar contrast media is recommended for CT studies to minimize adverse reactions.[18] Gadolinium contrast for MRI studies is not contraindicated in patients with a suspected pheochromocytoma.[19] CT findings in dogs with pheochromocytoma show a lobulated, irregularly shaped mass associated with the adrenal gland. Areas of decreased intensity are interspersed with highly vascular areas with increased intensity (Figures 74-1 and 74-2).[18] MRI may be used to differentiate between histologic types of adrenal tumors.[2] Scintigraphy using ^{123}iodinemetaiodobenzylguanidine (an NE analog) or ^{99m}technetium-methylene diphosphonate has been used in the dog to identify a pheochromocytoma.[20,21] One group used p-[^{18}F]fluorobenzylguanidine to identify tumors in dogs using positron emission tomography.[22] These techniques are useful for identifying metastatic tumors.

Laboratory test results in animals with a pheochromocytoma are generally unremarkable. In dogs, a mild nonregenerative anemia may be present secondary to chronic disease, or an increased mean cell volume or packed cell volume may be seen secondary to catecholamine or erythropoetin-like stimulation of the bone marrow.[1] A regenerative anemia may reflect hemorrhage from the tumor.[3] Leukocytosis or a stress leukogram may be found secondary to catecholamine release or inflammatory changes associated with the tumor.[2,3] If there has been hemorrhage or intravascular coagulation from the tumor, a consumptive thrombocytopenia may occur. Evidence of hypercoagulability may be present, but this has not been investigated in veterinary medicine (see Chapter 117, Hypercoagulable States).

Figure 74-2 Sagittal reconstruction of the helical computed tomography scan in Figure 74-1 showing invasion of the caudal vena cava along the length (4 cm) of the mass. Irregular filling of the cava is present cranial and caudal to the mass, likely representing thrombus formation. The cranial aspect of the caudal vena cava is denoted with an *arrow*.



Serum chemistry profiles may be normal, or may show elevations in liver enzymes (unrelated to liver metastasis).[3,7] Dogs with multiple endocrine neoplasia syndrome may be hypercalcemic as a result of elevated parathyroid hormone or parathyroid hormone–related peptide (PTH or PTH-rp). Dogs may be hyperglycemic from catecholamine stimulation of hepatic glucose production and decreased insulin release from α-receptor stimulation.[1] Pheochromocytomas may also secrete hormones such as vasoactive intestinal peptide, which may contribute to clinical signs such as diarrhea. In two retrospective reports of dogs with pheochromocytoma, hypercholesterolemia was present in 25% of dogs, possibly secondary to increased fat mobilization from catecholamine secretion or due to concurrent hyperadrenocorticism.[7,8]

In 20 dogs with a pheochromocytoma, but without concurrent disease, 50% showed proteinuria, likely caused by a hypertensive glomerulopathy.[2] Measurement of urinary catecholamine concentrations (metanephrine, normetanephrine, vanillylmandelic acid) as a spot check referenced to urine creatinine, or over a 24-hour period, is performed in humans with suspected pheochromocytomas and has been investigated in dogs.[7] Secondary factors, such as excitement, exercise, vanilla-containing foods, and radiographic contrast agents may result in false-positive elevations.[2]

Because of the similarity in clinical signs and ultrasonographic appearance of pheochromocytomas and adrenocortical tumors, and reports of the coexistence of hyperadrenocorticism and pheochromocytoma, hyperadrenocorticism should be ruled out at the time of medical workup.[8]

Other tests reported in humans include the clonidine suppression test, which should decrease serum catecholamine levels in normal patients but not in patients with a functional pheochromocytoma (because catecholamine release
from the tumor is not neurally mediated). The administration of intravenous phentolamine, an α-adrenergic 315
antagonist, to hypertensive patients will cause a decrease in blood pressure if the hypertension is catecholamine 316
mediated (close monitoring is vital). These tests have varying sensitivity and specificity, especially in the context of paroxysmal hypertension, and have not been evaluated thoroughly in veterinary patients.[2]

Provocation tests using metoclopramide, histamine, tyramine, and glucagon, all of which cause increased secretion of catecholamines from the tumor, are not recommended because of the potential for inducing acute hypertensive crises.[2] For this reason, the use of metoclopramide as an antiemetic in patients with suspected pheochromocytoma may be contraindicated.

Because hypertension and tachycardia may be paroxysmal, blood pressure and electrocardiogram (ECG) monitoring should be performed, but results may be low yield. Holter or continuous ECG monitoring may be necessary for the diagnosis of intermittent tachyarrhythmias.

The results of a biopsy or fine-needle aspiration of adrenal tumor masses are not discussed at length in the literature. This may be partially due to the difficulty of safely obtaining samples, or because excisional biopsy is preferred. Gilson and others note a similarity in cytologic appearance between lymphosarcoma and pheochromocytoma when diagnosed from ascitic fluid in three dogs, so an adequate index of suspicion is necessary to prevent misdiagnosis.[7] Impression smears of a pheochromocytoma may also appear similar to a round cell tumor.[5] In addition, it is difficult to characterize relative malignancy on the basis of histopathologic evaluation, so it may be difficult to accurately predict tumor behavior on the basis of biopsy specimens.[7] Any tumor that demonstrates invasion of adjacent structures should be considered malignant.

74.5 TREATMENT

Definitive treatment for pheochromocytoma is surgical excision. Surgery is often complicated, and may necessitate vena caval venotomy or nephrectomy to fully remove or debulk the tumor. A recent study found an overall mortality rate of 22% after removal of adrenal tumors in dogs, which was not correlated with vena caval invasion or tumor type.[17] A thorough abdominal exploration is recommended during surgery to identify gross metastatic disease. In a study of 61 dogs, 15% showed metastasis and 39% had locally invasive tumors.[8] In this study, concurrent neoplasia of various cellular origins was identified in 54% of the dogs.

Noncompetitive α-adrenergic blockade with phenoxybenzamine (0.5 to 2.5 mg/kg PO q12h) should be instituted at least 1 week before anesthesia for surgical resection of the tumor. This may help to blunt hypertensive episodes during anesthesia, although high dosages may be necessary.[17] In humans, preoperative α-adrenergic blockade decreased perioperative mortality associated with resection of pheochromocytoma from 13% to 45% to 0 to 3%.[25] α-Methyl-para-tyrosine competitively inhibits tyrosine hydroxylase, interfering with catecholamine biosynthesis.[23] It may be a useful drug for patients with pheochromocytoma, although there are limited reports of its use in dogs or cats, none of which had a pheochromocytoma.

Chronic sympathetic stimulation and vasoconstriction may result in intravascular volume depletion, which should be assessed and corrected before the induction of anesthesia.

Anticholinergic drugs that cause tachycardia and barbiturate agents that may cause ventricular arrhythmias in the presence of excess catecholamines should be avoided for anesthetic premedication and induction. Long-lasting α-adrenergic antagonists such as acepromazine may complicate intraoperative or postoperative treatment and should be avoided, especially if the animal has been pretreated with phenoxybenzamine. A safe induction protocol includes an opioid, such as oxymorphone, hydromorphone, or fentanyl (minimal histamine release), combined with a benzodiazepine and propofol or etomidate to facilitate endotracheal intubation. Inhalant agents such as isoflurane or sevoflurane are preferred to halothane, which sensitizes the myocardium to catecholamine-induced arrhythmias. Desflurane can cause sympathetic stimulation and should be avoided. There are no contraindications to the use of nitrous oxide in humans undergoing surgery for pheochromocytoma.[23] Inhalant agents may be supplemented with balanced anesthetic techniques using potent opioids such as fentanyl, administered as a constant rate infusion (0.7 to 2 μg/kg/min).

Intraoperative monitoring must include ECG and arterial blood pressure (preferably direct), as well as central venous pressure to estimate intravascular volume. Pulmonary arterial catheterization will give information about cardiac output and systemic vascular resistance that may help to tailor fluid and drug therapy during and after surgery; however, placement of these catheters may be associated with increased morbidity (see Chapter 50, Pulmonary Artery Catheterization).[23]

During anesthesia, treatment with short-acting β-blocking drugs such as esmolol (0.1 to 0.5 mg/kg IV followed by 0.5 to 2 μg/kg/min IV), or vasodilators such as nitroprusside (0.2 to 10 μg/kg/min IV), may be necessary to maintain normal hemodynamics (see Chapters 178 and 191, Antihypertensives and β-Blockers, respectively). Some human reports advocate magnesium sulfate for vasodilation during surgery for pheochromocytoma.[24] Supraventricular tachycardia (SVT) is a common arrhythmia during surgery, although bradycardia with atrioventricular block and ventricular premature complexes have also been seen. Lidocaine may be used to treat ventricular arrhythmias (see Chapter 190, Antiarrhythmic Agents). Before surgery, blood type and crossmatch to multiple units of packed red blood cells or fresh whole blood should be performed in case of severe intraoperative hemorrhage. Blood pressure during anesthesia in the hypertensive animal should be maintained at levels close to its resting blood pressure to prevent renal hypoperfusion, and urine output should be measured intraoperatively. If a venotomy is anticipated for removal of a thrombus, external cooling of the patient may be of benefit to protect tissues during intraoperative interruption of blood flow and ischemia.[16] Surgical manipulation of the tumor may cause catecholamine release. Alternatively, removal of the tumor may result in cardiovascular collapse from lack of catecholamines, requiring supplementation with sympathomimetic drugs such as phenylephrine (0.5 to 10 μg/kg/min IV) or norepinephrine (0.1 to 3 μg/kg/min IV) (see Chapter 176, Vasoactive Catecholamines).

Postoperatively, hypertension may or may not resolve, even with full excision of the tumor.[7] If bilateral adrenalectomy has been performed, supplementation with glucocorticoids and mineralocorticoids will be necessary. Postoperative hypotension or cardiovascular collapse is possible, and a decreased sensitivity to catecholamines from chronic stimulation may require noncatecholamine pressors such as vasopressin to maintain adequate blood pressure.[25] Blood glucose should be monitored postoperatively, because the removal of sympathetic stimulation may cause hypoglycemia.

Functional adrenocortical tumors may be associated with pulmonary thromboembolic disease; however, the association in the context of pheochromocytoma is unclear. If an animal is suspected to be hypercoagulable, postoperative anticoagulation with heparin may be indicated.

In animals with symptomatic pheochromocytomas that are nonresectable or metastatic, in which surgical resection is not likely to be successful, medical treatment with phenoxybenzamine, oral β-blockers, or other antiarrhythmic agents is indicated to alleviate some clinical signs. β-Blockers should not be administered without concurrent α-blockade, because the loss of β_2-receptor–mediated vasodilation may exacerbate hypertension. Other therapy directed more specifically toward the clinical signs (e.g., diuretics to treat ascites) may also be indicated. Chemotherapeutic or radiotherapeutic treatment of pheochromocytoma in small animals has not been reported; however, it has been unrewarding in human medicine.[5]

74.6 PROGNOSIS

Extensive information on prognosis after surgical resection or medical treatment of pheochromocytoma is not available. According to the studies that have been published, larger tumors with invasion of neighboring structures may indicate a poorer prognosis. Gilson reported that factors such as neurologic deficits, weight loss, and abdominal distention may be associated with a poorer prognosis in dogs.[7] In humans, histopathologic analysis which shows multiploidy (e.g., aneuploidy or tetraploidy) in the nuclear DNA of the tumor cells has been associated with poorer prognosis.[26]

With complete resection and uneventful recovery from surgery, even dogs with vena caval thrombi may experience significant survival, reported from 18 months to 3 years.[2,8,16] Many dogs, however, experience significant complications during the first 24 to 72 hours postoperatively.[16] In one study, 51% (20 of 39) dogs experienced postoperative complications after resection of adrenal tumors. These included ventricular tachyarrhythmias, dyspnea, disseminated intravascular coagulopathy, abdominal incisional dehiscence, internal hemorrhage, and vomiting.[16] One dog in this group experienced refractory hypertension after removal of a pheochromocytoma. Tumor type (adrenocortical versus pheochromocytoma) or presence of caval thrombi was not related to complications. Seven of eleven dogs with pheochromocytoma experienced perioperative morbidity after resection of the tumor.[16]

In the limited studies available, recurrence of primary tumor or of metastatic disease is rare.[8] In the nine dogs that survived surgical resection of a pheochromocytoma in the study by Kyles and colleagues recurrence of clinical signs or tumor-related death was not reported, with a median follow-up time of 9 months (range from 1 to 36 months).[16]

74.7 SUGGESTED FURTHER READING*

PY Barthez, SL Marks, J Woo, et al.: Pheochromocytoma in dogs: 61 cases (1984-1995). *J Vet Intern Med*. **11**, 1997, 272, *Veterinary retrospective study on incidence of pheochromocytoma in dogs, with a review of clinical signs and coexisting conditions*.

MAO Kinney, BJ Narr, MA Warner: Perioperative management of pheochromocytoma. *J Cardiothorac Vasc Anesth*. **16**, 2002, 359, *An excellent human review of anesthetic management of pheochromocytoma*.

A Kyles, E Feldman, H De Cock, et al.: Surgical management of adrenal gland tumor with and without associated tumor thrombi in 40 dogs (1994-2001). *J Am Vet Med Assoc*. **223**, 2003, 654, *Excellent article describing advanced surgical and anesthetic management of dogs with adrenal masses*.

DS Rosenstein: Diagnostic imaging in canine pheochromocytoma. *Vet Radiol Ultrasound*. **41**, 2000, 499, *Article that discusses various imaging modalities for the adrenal mass*.

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* See the CD-ROM for a complete list of references

75 Chapter 75 Relative Adrenal Insufficiency

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75.1 KEY POINTS

- Cortisol is an important hormone involved in modulation of inflammation and regulation of vascular tone.
- Relative adrenal insufficiency (RAI) is common in humans with sepsis and other types of critical illness.
- Human patients with RAI have poor vascular responsiveness and worse survival than those with normal hypothalamic-pituitary-adrenal axis (HPA) function.
- The best method for diagnosing RAI is unknown.
- Low dosages of hydrocortisone improve pressor responsiveness and survival in humans with RAI and septic shock.
- RAI likely occurs in a subpopulation of critically ill dogs and cats.
- Appropriate methods for the diagnosis and management of RAI in dogs and cats are unknown.

75.2 INTRODUCTION

Cortisol is a hormone released by the adrenal glands in small amounts in a circadian rhythm, and in larger amounts during times of physiologic stress. It has many important homeostatic functions including regulation of carbohydrate, lipid, and protein metabolism; immune system modulation; ensuring proper production of catecholamines and function of adrenergic receptors; and stabilizing cell membranes. A classic example demonstrating the importance of cortisol function is the patient with glucocorticoid-only hypoadrenocorticism. Patients with minimal endogenous corticosteroid production show clinical signs of gastrointestinal disturbance, weight loss, and collapse, particularly in stressful situations. These patients can be treated successfully with glucocorticoid supplementation.

Serum cortisol concentration is determined by the hormonal cascade and negative feedback mechanisms of the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus produces corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH). ACTH in circulation stimulates the zona fasciculata and zona reticularis of the adrenal gland to produce and release cortisol. Cortisol has negative feedback action on both the hypothalamic release of CRH and the pituitary release of ACTH. Thus, when circulating cortisol concentration is low, CRH and ACTH will increase, stimulating the adrenal glands to produce more cortisol. The increased serum cortisol concentration inhibits the release of more CRH and ACTH.

Research over the past decade has shown that abnormalities of HPA axis function are common in human patients with severe sepsis and septic shock, conditions that frequently carry a mortality rate of 50% or more in both human and veterinary medicine.[1-5] Many well-conceived and well-performed clinical studies have found RAI, also called *critical illness-related corticosteroid insufficiency (CIRCI),* in up to 77% of human patients with severe sepsis and septic shock.[1,6-9] Unlike patients with classic hypoadrenocorticism, those with critical illness-associated RAI usually have normal to elevated basal serum cortisol concentration, but a blunted cortisol response to an ACTH stimulation test. Therefore their adrenal dysfunction truly is relative—it is believed that although the adrenal glands can make and release cortisol, the quantity is inadequate for the degree of physiologic stress. Following recovery from sepsis, HPA axis dysfunction resolves.[10]

75.3 ASSOCIATED PRIMARY ILLNESSES

Patients with relative adrenal insufficiency (RAI) include humans with severe sepsis and septic shock,[1,6-9] severe hepatic disease,[11] acute myocardial infarction,[12] and hemorrhagic shock.[13] It is important to note that although many illnesses are associated with RAI, all humans who have RAI are critically ill; RAI has not been documented in patients with localized infections, mild to moderate hepatopathy, or stable heart disease.

75.4 SUSPECTED PATHOPHYSIOLOGY

The underlying mechanisms of RAI are unknown. Studies have suggested that the inflammatory cytokines interleukin-6[14,15] or tumor necrosis factor,[16,17] or corticostatin peptides produced by immune cells[18] may interfere with HPA axis function. Also, there have been reports of RAI associated with adrenal hemorrhage in critically ill humans.[19,20] Adrenal hypoperfusion and microvascular disease from disseminated intravascular coagulation may contribute. Even if glucocorticoids are produced in adequate amounts in critically ill patients, they may not be able to exert their effects. There is evidence that corticosteroid receptor numbers may be decreased in patients with hemorrhagic and septic shock.[21] Cytokines may cause corticosteroid receptor dysfunction.[22]

75.5 SPECIES AFFECTED

It is widely accepted that RAI occurs in critically ill humans but strong evidence of RAI does not yet exist in veterinary medicine. One study of 20 dogs sequentially admitted to a veterinary intensive care unit failed to find HPA axis abnormalities in any patients,[23] although another study in critically ill septic dogs found a 48% incidence of RAI.[24] A study in cats admitted to an intensive care unit did not demonstrate RAI in septic cats, but did find HPA axis abnormalities in cats with neoplasia.[25] Another study showed a decreased response to exogenous ACTH in septic cats compared with a group of normal cats.[26] Thus it appears that RAI probably occurs in some subpopulations of critically ill dogs and cats. Clinical evidence in other species is unavailable.

75.6 CLINICAL MANIFESTATIONS

The most common clinical abnormality associated with RAI in humans with septic shock is hypotension refractory to fluid loading. Studies have shown that RAI is associated with decreased pressor responsiveness in human patients that is reversed with glucocorticoid administration.[27] In vitro studies have shown that smooth muscle adrenergic receptor expression is modulated by glucocorticoids.[28,29] One human clinical study showed that myocardial adrenergic receptor down-regulation in shock could be reversed by glucocorticoids.[30] Another study investigating the phenylephrine–mean arterial pressure relationship in humans with septic shock showed that physiologic dosages of hydrocortisone normalized vasomotor response to the drug,[31] underscoring the clinical importance of glucocorticoids in smooth muscle response to catecholamines.

Human patients with RAI may be more likely to die than those with similar illness severity and an intact HPA axis.[32-34] Preliminary data from a study in septic dogs suggests that those with RAI may be more likely to die than those with normal HPA function.[24]

75.7 DIAGNOSIS

There is no consensus in the human medical community regarding the identification of patients with RAI. A variety of tests have been used, including basal cortisol concentration, ACTH-stimulated cortisol concentration, the difference in cortisol concentration when subtracting baseline from stimulated cortisol concentration (δ-cortisol), the relationship between endogenous ACTH concentration and basal cortisol concentration, and combinations of these methods. When stimulated or δ-cortisol concentration is used in the diagnosis, questions remain regarding the appropriate dosage of synthetic ACTH to be administered. Many human studies have used a single 250-μg injection,[1,7,9] but some authors suggest using a total dosage of 1 μg per adult human.[35] Studies have found differences in the incidence of RAI depending on whether they administer a 250-μg or a 1-μg dose of ACTH, thus further complicating the diagnosis.[6,8]

The best way to identify critically ill patients with HPA axis dysfunction is unclear. Indeed, it is unknown for any individual exactly how much cortisol is needed or optimal for a given severity of illness. Hence, the diagnosis of RAI from a population perspective may ultimately prove impossible.

75.7.1 Human Data

A study in humans with septic shock found that a baseline cortisol level less than or equal to 34 μg/dl combined with a δ-cortisol level of 9 μg/dl or more in response to 250 μg ACTH was associated with a relatively good prognosis (28-day mortality 26%), although baseline cortisol concentration over 34 μg/dl combined with a δ-cortisol level of less than 9 μg/dl was associated with a very poor prognosis (28-day mortality 82%).[34] Likely because this protocol successfully predicted outcome, the 250-μg ACTH stimulation test is commonly used to diagnose RAI in human medicine. Blood is collected for basal serum cortisol concentration, contents of a single 250-μg vial of synthetic ACTH is injected intravenously, and a poststimulation cortisol concentration is determined 1 hour later. The basal cortisol concentration is then subtracted from the stimulated value, which yields the δ-cortisol value. In humans, a δ-cortisol concentration of less than 250 nmol/L (<9 μg/dl) is generally considered diagnostic for RAI, although many studies have used different criteria.

75.7.2 Veterinary Data

No clinical veterinary studies have been performed to determine how best to diagnose RAI in dogs and cats. Although studies exist in the veterinary literature investigating the presence of RAI in these species, none of the investigations has surveyed critically ill patients to see if there is a specific HPA axis abnormality associated with increased mortality. We have performed a study to determine whether RAI occurs in dogs with sepsis using a standard 1-hour 250-μg ACTH stimulation test. As part of this study, we performed ACTH stimulation tests in a group of normal dogs, then arbitrarily used a δ-cortisol level one-half that of the lowest control dog (δ-cortisol 5.7 μg/dl) to define RAI. Using this definition, we found that a δ-cortisol concentration less than or equal to 2.8 μg/dl in septic dogs was associated with nonsurvival when compared with dogs with δ-cortisol values more than 2.8 μg/dl.[24] Therefore using the δ-cortisol cutoff value of 2.8 μg/dl may be an appropriate preliminary method for diagnosing RAI in septic dogs, because it appears to be associated with outcome. Note, however, that the cutoff of 2.8 μg/dl was arbitrary and likely does not represent the best value for diagnosis. Further study of larger populations of critically ill dogs is required to determine the best way to diagnose RAI in this population.

The studies performed in cats have used basal cortisol concentrations, stimulated cortisol concentrations, and δ-cortisol values. The ACTH stimulation test was performed using 125 μg synthetic ACTH injected intravenously with samples collected 1 hour later for determination of poststimulated cortisol concentration.[25,26] A cutoff value for RAI was not proposed in either study, but Costello and colleagues found that septic cats had a mean δ-cortisol value of 2.3 μg/dl (SD ± 2.5 μg/dl) whereas the mean δ-cortisol concentration in normal cats was 6.5 μg/dl (SD ± 4.6).[26] Note that although the mean δ-cortisol value in septic cats was significantly lower than that in normal cats, the ranges likely overlap. Thus, although RAI appears to occur in cats, appropriate diagnostic criteria are undetermined.

75.8 TREATMENT

75.8.1 Human Data

Human patients with documented RAI that are treated with supplemental doses of hydrocortisone are more likely to be weaned from pressors* and ultimately survive[1,9,11] than patients with RAI that do not receive steroid supplementation. Studies over the decades have repeatedly failed to show benefit when large dosages of steroids (i.e., 30 to 120 mg/kg methylprednisolone per day) are used in septic patients. These high dosages for septic human and veterinary patients are out of favor, because their use is not supported by clinical evidence.[38-40] The dosages of steroids used to manage RAI are significantly smaller, called *supplemental, physiologic, low-dosage,* or *replacement* in the literature. Most human studies have used a protocol of 200 to 300 mg q24h of hydrocortisone for a 70-kg human (2.9 to 4.3 mg/kg q24h). Hydrocortisone is one-fourth as potent as prednisone and one thirtieth as potent as dexamethasone. Therefore this supplemental steroid dosage is 0.7 to 1 mg/kg q24h of prednisone equivalent or 0.1 to 0.4 mg/kg q24h of dexamethasone equivalent. Thus one can see how much lower these steroid dosages are than those commonly used for treatment of endotoxemia and shock.[41] The higher dosages are not supported by clinical evidence and should not be used.

Human studies have used various protocols to administer the 200 to 300 mg hydrocortisone q24h. Some studies have divided the total daily hydrocortisone dosage into four equal bolus doses every 6 hours, and others have started with an initial dosage of 0.7 mg/kg hydrocortisone as a bolus followed by a constant rate infusion to attain total daily dosage from that point forward.

* References 1, 6, 9, 11, 36, 37.

75.8.2 Veterinary Data

There is no clinical evidence to determine whether dogs and cats with RAI would benefit from low-dosage steroid supplementation. In our hospital, dogs and cats with septic shock (hypotension despite adequate fluid loading determined by central venous pressure or pulmonary artery occlusion pressure measurements) are treated at the clinician's discretion with 2.9 to 4.3 mg/kg q24h of hydrocortisone after undergoing a standard 1-hour ACTH stimulation test. This total daily dosage is split into four equal intravenous doses given every 6 hours. It seems reasonable to continue steroid therapy only in patients who have either a low δ-cortisol concentration (≤2.8 μg/dl for dogs; unknown for cats) or in those that show significant improvement in cardiovascular status within 24 hours of starting the drug. We have no direct clinical evidence to support the use of steroids in veterinary patients.

75.9 PROGNOSIS

Human patients with RAI have a worse prognosis than those with normal HPA axis function. However, with supplemental hydrocortisone therapy, patients with RAI may have the same prognosis as those with normal HPA axis function and the same severity of illness.[1] If the patient survives the primary underlying illness, prognosis for return of normal HPA axis function is good.[10]

75.10 SUGGESTED FURTHER READING*

D Annane, V Sebille, C Charpentier, et al.: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *J Am Med Assoc*. **288**, 2002, 862, *Landmark paper that demonstrated that physiologic hydrocortisone significantly improves 28-day survival in humans with septic shock who suffer from adrenal insufficiency. No improvement in survival with hydrocortisone therapy in patients with normal HPA axes*.

D Annane, V Sebille, G Troche, et al.: A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *J Am Med Assoc*. **283**, 2000, 1038, *A study that showed a significant correlation between various HPA axis parameters and outcome; the study generally cited as the grounds for using the δ-cortisol value to define RAI in critically ill humans*.

JM Burkitt, SC Haskins, RW Nelson: Relative adrenal insufficiency in dogs with sepsis. *J Vet Intern Med*. **21**, 2007, 226, *A prospective study of 33 dogs from a small animal intensive care unit that demonstrated the presence of relative adrenal insufficiency in a subset of dogs with sepsis. Dogs with RAI were more likely to be hypotensive and more likely to die than those that had normal HPA axis function*.

MF Costello, DJ Fletcher, DC Silverstein, KJ Drobatz: In *Adrenal insufficiency in feline sepsis*. 2006, ACVECC, San Francisco, ACVECC postgraduate course 2006: Sepsis in veterinary medicine *Data from this study presented at the 2005 International Veterinary and Critical Care Symposium in Atlanta, Georgia, suggesting the presence of RAI in septic cats*.

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* See the CD-ROM for a complete list of references

76 Chapter 76 Hypoadrenocorticism

Jamie M. Burkitt, DVM, DACVECC

76.1 KEY POINTS

- Hypoadrenocorticism is uncommon in the dog and rare in the cat.
- Primary hypoadrenocorticism is due to failure of the adrenal glands, whereas secondary hypoadrenocorticism is due to pituitary or hypothalamic malfunction.
- Young to middle-aged female dogs are predisposed.
- Certain breeds are overrepresented, but most dogs with Addison's disease are of mixed breeding.
- Diagnosis is challenging because signs and clinicopathologic findings of hypoadrenocorticism mimic many other disease processes.
- Definitive diagnosis is by adrenocorticotropic hormone (ACTH) stimulation test, ideally coupled with an endogenous ACTH concentration.
- Treatment of the animal in crisis consists of aggressive, appropriate fluid resuscitation followed by hormone replacement.
- Electrocardiographic (ECG) changes associated with hyperkalemia can be life threatening and must be treated promptly and appropriately.
- Cats may require 3 to 5 days for a good clinical response to therapy.
- Long-term prognosis is very good with lifelong hormone supplementation.

76.2 INTRODUCTION

The adrenal cortex is responsible for secreting many important hormones including cortisol and aldosterone. Cortisol is a glucocorticoid released in small amounts in a circadian rhythm, and in larger amounts during times of physiologic stress. It has many important homeostatic functions including regulation of carbohydrate, lipid, and protein metabolism; modulation of immune system function; ensuring proper production of catecholamines and function of adrenergic receptors; and stabilizing cell membranes. Serum cortisol concentration is determined by the hormonal cascade and negative feedback mechanisms of the hypothalamic-pituitary-adrenal axis. The hypothalamus produces corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH). ACTH in circulation stimulates the zona fasciculata and zona reticularis of the adrenal cortex to produce and release cortisol. Cortisol has negative feedback action on both the hypothalamic release of CRH and the pituitary release of ACTH. Thus, when circulating cortisol concentration is low, CRH and ACTH will increase, stimulating the adrenal glands to produce more cortisol. The increased serum cortisol concentration inhibits the release of more CRH and ACTH.

Aldosterone is a mineralocorticoid released from the zona glomerulosa of the adrenal cortex under the influence of a complex hormonal cascade that starts in the kidney. Its main purposes are to maintain normovolemia and enhance potassium excretion. When effective circulating volume is depleted, glomerular filtration decreases. The macula densa, a group of specialized cells in the distal portion of the thick ascending loop of Henle, senses decreased filtrate (specifically chloride) delivery. The macula densa then induces renin release from the nearby juxtaglomerular cells of the afferent arteriole serving that nephron. Renin cleaves the circulating hormone angiotensinogen into angiotensin I. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme located in the lung, on endothelial cells throughout the body, and in many other organs. Angiotensin II stimulates the zona glomerulosa to release aldosterone, which stimulates cells of the renal collecting duct to reabsorb sodium and excrete potassium. Sodium reabsorption leads to water retention and thus augmentation of effective circulating volume. The adrenal cortex also releases a significant amount of aldosterone in response to hyperkalemia and a minimal amount in response to ACTH.

Hypoadrenocorticism, also called *Addison's disease,* is an uncommon disease in dogs and is rare in cats. Primary hypoadrenocorticism is caused by adrenal gland dysfunction, whereas secondary hypoadrenocorticism occurs when hypothalamic or pituitary malfunction prevents the release of CRH or ACTH, respectively. In most cases, patients with primary hypoadrenocorticism will have both glucocorticoid and mineralocorticoid insufficiency. However, there are many reports of dogs with atypical primary hypoadrenocorticism who have only glucocorticoid insufficiency.[1-4] Dogs with atypical primary hypoadrenocorticism may progress to mineralocorticoid deficiency within months of initial diagnosis.[1,2,4] Because aldosterone release is mediated primarily by the renin-angiotensin cascade and serum potassium concentration, patients with secondary hypoadrenocorticism do not usually have the classic electrolyte abnormalities seen in patients with typical primary hypoadrenocorticism (see Clinicopathologic Findings).

76.3 WHO IS AFFECTED?

Hypoadrenocorticism usually occurs in young to middle-aged dogs, and females are more commonly affected than males.[2,4-7] Although the average age of onset is approximately 4 years,[4-7] naturally occurring hypoadrenocorticism has been documented in dogs as young as 4 months,[5,8] as well as in geriatric dogs. The most commonly affected pure breeds vary somewhat by report and include the Portuguese Water Dog, Great Dane, West Highland White Terrier, Standard Poodle, Wheaton Terrier, and Rottweiler.[5] It is important to note that mixed breed dogs are more commonly affected than any individual breed.[4,5] Primary hypoadrenocorticism has been reported in fewer than 40 cats. There appears to be no sex predilection in this species, and most are domestic shorthaired or longhaired cats.[4,9-13] Most cats are young to middle aged, with ages ranging from 1.5 to 14 years.[11]

76.4 ETIOLOGY

The cause of naturally occurring primary hypoadrenocorticism in dogs and cats is unknown, but the most widely accepted theory is one of immune-mediated destruction of the adrenal cortices.[4,6] In support of this theory, young to middle-aged female dogs are most commonly affected by both Addison's disease and established immune-mediated diseases, and naturally occurring primary hypoadrenocorticism in humans is caused by immune-mediated destruction of the adrenal cortices. On necropsy, adrenal glands of affected animals are atrophied and fibrosed, consistent with prior immune-mediated destruction.[4,6,9,11] Other documented causes of primary hypoadrenocorticism in dogs and cats include adrenal neoplastic infiltration,[14,15] trauma,[16] suspected hemorrhage or hypoperfusion,[17] and iatrogenic destruction due to mitotane[18] or trilostane[19] therapy for hyperadrenocorticism. Adrenal infiltration with infectious organisms has also been implicated.[4]

Secondary hypoadrenocorticism is due to hypothalamic or pituitary malfunction; decreased CRH or ACTH secretion causes decreased adrenal cortisol production. The most common cause of secondary hypoadrenocorticism is steroid withdrawal after long-term glucocorticoid therapy.[4,20] Long-term steroid administration causes negative feedback on the hypothalamus and pituitary, significantly decreasing ACTH production, which leads to adrenal cortical atrophy. Other documented causes of secondary hypoadrenocorticism in dogs and cats include hypothalamic or pituitary neoplasia,[21] trauma,[22] and iatrogenesis (surgical).

76.5 CLINICAL PRESENTATION

The most important thing to remember about hypoadrenocorticism is that the clinical picture is vague and mimics other disease processes, most of which are significantly more common than Addison's disease. The classic signs and basic diagnostic test results in the hypoadrenal patient are generally nonspecific, and the vast majority of Addisonian patients will not have all the classic signs. Therefore the clinician must always remember to place hypoadrenocorticism on the rule-out list for the patient that has any of these clinical signs.

76.5.1 History

The history for patients with Addison's disease is often vague and nonspecific, and usually includes decreased appetite, lethargy, gastrointestinal (GI) disturbance, and weight loss. GI bleeding manifested by hematemesis, hematochezia, or melena may be present.[1,3,4,7,23] Other historical findings may include polyuria, polydipsia, weakness, shaking, pain, muscle cramps, and other nonspecific problems.[1,4-6,24] Because the clinical signs are often vague, patients may be brought for treatment in acute crisis without specific prior clinical signs. Thus the absence of such signs does not exclude hypoadrenocorticism as a diagnosis.

76.5.2 Physical Examination

Physical examination findings can vary significantly, depending on whether the hypoadrenocorticism involves hypoaldosteronism and on the severity and duration of illness. The most common physical examination findings include lethargy, weakness, poor body or coat condition, and dehydration. Collapse, hypovolemic shock, GI bleeding, abdominal pain, bradycardia, and hypothermia are common (particularly in emergency and critical care practice), although not all these abnormalities should be expected concurrently in any individual.[1,4-7,11] Patients with secondary hypoadrenocorticism or atypical primary hypoadrenocorticism may be less likely to arrive in crisis, because these patients have adequate aldosterone to maintain intravascular volume and normal electrolyte concentrations.[1,3,4]

76.5.3 Clinicopathologic Findings

The most common clinicopathologic findings are a decrease in the sodium-to-potassium ratio, azotemia with an inappropriately low urine specific gravity, anemia, and a leukogram inconsistent with the patient's degree of illness. The normal sodium-to-potassium ratio is 27:1 to 40:1. Patients with typical primary hypoadrenocorticism (i.e., with aldosterone insufficiency) usually have a pretreatment sodium-to-potassium ratio of less than 27:1. Note that these patients need not have both hyponatremia and hyperkalemia[2]; rather, some have only one of these abnormalities, and the ratio of these cations can still be less than 27:1. Patients with only glucocorticoid insufficiency are unlikely to have these electrolyte changes.[1-4] Many other diseases and conditions occasionally have been associated with low sodium-to-potassium ratios, including renal failure or postrenal obstruction,[25,26] severe GI disease,[4,26,27] parasitic infestation,[25,27,28] pregnancy,[29] body cavity effusions,[26] and others.[4,26] Note that although a low sodium-to-potassium ratio is the classic electrolyte abnormality of Addison's disease, not all patients with hypoadrenocorticism will have this change, which may be present with other conditions.

Most Addisonian patients are azotemic and hyperphosphatemic on arrival.[4-7,11] These changes are generally attributed to hypovolemia and are therefore prerenal in origin. However, most dogs and cats with hypoadrenocorticism have inappropriately low urine specific gravity (i.e., <1.030). Inability to appropriately concentrate urine has been attributed to lack of sodium retention and resultant renal medullary washout.[4,30] Renal concentrating ability resolves with mineralocorticoid supplementation.

The complete blood count (CBC) usually reveals a mild to moderate nonregenerative anemia due to lack of cortisol tropism at the level of the bone marrow. Patients with significant concomitant GI bleeding can have severe anemia that may be nonregenerative.[23] The degree of anemia may be masked initially by dehydration and resultant hemoconcentration. The CBC may reveal a “reverse stress leukogram,” with relative or absolute neutropenia, lymphocytosis, and eosinophilia; however, the Addisonian patient can also have the neutrophilia and lymphopenia commonly seen with severe illness. Addisonian patients frequently have very normal-appearing CBC findings. It is very important to interpret the CBC values in light of the severity of disease; a normal CBC result or the “reverse stress leukogram” in an ill patient should always raise the clinician's suspicion for hypoadrenocorticism.

Other blood work may reveal hypoglycemia, hypercalcemia, metabolic acidosis, hypoalbuminemia, and hypocholesterolemia. Hypoglycemia has been reported in up to 38% of dogs with hypoadrenocorticism.[1,4-7] Cortisol promotes glycogenolysis and gluconeogenesis, and lack of these processes may cause the hypoglycemia seen in some Addisonian patients. Seizures have been reported as a result of severe hypoglycemia in hypoadrenocorticism.[31,32] It is important to note that hyperglycemia has also been reported in dogs with hypoadrenocorticism,[4-7] so its presence does not exclude the diagnosis. Hypercalcemia has been reported in dogs and cats with hypoadrenocorticism[1,4-7,11,20,33]; its mechanism is unclear. Metabolic acidosis is seen commonly in dogs with hypoadrenocorticism. The acidosis is attributed to hypovolemia, with its resultant lactic acidosis, and decreased renal tubular hydrogen ion excretion, which is enhanced by aldosterone. Hypoalbuminemia has been reported in dogs with hypoadrenocorticism; the mechanism is unclear, but it may be related to GI bleeding, protein-losing enteropathy, or decreased hepatic synthesis.[4,34] Lastly, hypocholesterolemia has been reported in association with hypoadrenocorticism.[1,4,5,7] Elevated cholesterol concentration has also been reported in these patients; thus its importance in the diagnosis is equivocal. The most important feature of the basic clinicopathologic data in the hypoadrenal patient is its highly variable nature. One should not expect to find all the classic clinicopathologic changes in one animal.

76.5.4 Electrocardiographic Findings

An electrocardiogram (ECG) should be performed in all patients with clinical signs of hypovolemia or established hyperkalemia. Hypoadrenal patients may have bradycardia, which can be seen with or without hyperkalemia.[1,4,7] Those with hyperkalemia may have bradycardia, diminished or absent P waves, “tented” T waves, wide or bizarre QRS complexes, ventricular fibrillation, or asystole. Ventricular fibrillation and asystole require immediate cardiopulmonary resuscitation (see Chapter 4, Cardiopulmonary Resuscitation). All hyperkalemia-related ECG changes are of immediate life-threatening importance and should be treated promptly and appropriately (see Chapter 55, Potassium Disorders). Before using insulin to treat hyperkalemic ECG abnormalities, make sure the patient is not already hypoglycemic and that glucose supplementation is adequate.

76.5.5 Diagnostic Imaging

Radiographic findings in patients with hypoadrenocorticism may include microcardia, decreased size of pulmonary vasculature, small caudal vena cava, and microhepatica.[5,7,11,35] Although one study found that approximately 80% of dogs in Addisonian crisis had at least one of these radiographic abnormalities,[35] it is important to remember that many hypoadrenal patients will have normal radiographic findings. Abdominal ultrasonographic findings may reveal small adrenal glands bilaterally.[36] Because of the difficulty in locating normal adrenal glands in many animals, size interpretations should be made only by people highly trained and experienced in veterinary abdominal ultrasonography.

76.6 DIAGNOSIS

Although the above clinical picture with its accompanying biochemical and CBC changes should increase the clinician's suspicion of hypoadrenocorticism, a definitive diagnosis is made by the ACTH stimulation test. A standard ACTH stimulation test is performed using 250 μg cosyntropin per dog or 125 μg cosyntropin per cat; the drug can be given intramuscularly or intravenously. Blood is collected for serum cortisol measurement prior to ACTH administration, and after 60 minutes in the dog, and after both 30 and 60 minutes in the cat.[4] If cosyntropin is not available, ACTH gel can be used. The protocol is 2.2 IU/kg ACTH gel IM in dogs and cats. Cortisol measurements are made before and 2 hours after ACTH administration in dogs and before and 1 and 2 hours after administration in cats.[4] Contact a veterinary reference laboratory for appropriate sample handling techniques, which can significantly alter the results.

Endogenous ACTH concentration is useful in differentiating primary from secondary hypoadrenocorticism. The distinction is particularly important in Addisonian patients with normal electrolyte values: if they have low endogenous ACTH concentration, they have secondary hypoadrenocorticism (hypothalamic or pituitary malfunction) and are unlikely to develop mineralocorticoid deficiency. However, the hypoadrenal patient with normal electrolyte values and an elevated endogenous ACTH concentration (atypical primary hypoadrenocorticism) may develop mineralocorticoid deficiency over time and therefore requires close monitoring. The sample for endogenous ACTH concentration should be taken along with the sample for baseline cortisol, before exogenous ACTH administration. Contact a veterinary reference laboratory for appropriate sample handling techniques, which can alter the results significantly.

Most exogenously administered glucocorticoids will interfere with adrenal function testing, affecting baseline cortisol, stimulated cortisol, and endogenous ACTH concentrations. Therefore, if the patient has a history of recent steroid administration, the tests should be delayed while glucocorticoids are withheld and the patient is treated symptomatically. The patient in crisis requires fluid resuscitation first and foremost; it is appropriate to collect an endogenous ACTH sample and complete the ACTH stimulation test before administration of supplemental steroids.

76.7 TREATMENT

By far the most important treatment for patients with hypoadrenocorticism is adequate and appropriate IV fluid therapy. Patients presenting to the emergency or intensive care setting are likely to be in crisis. Patients should be treated for shock as their physical examination and intensive monitoring results dictate (see Chapters 10 and 65, Shock and Shock Fluids and Fluid Challenge, respectively).

76.7.1 Fluid Therapy

Traditionally, 0.9% saline has been recommended for initial fluid treatment of Addisonian patients, because it has fluid and sodium to replace fluid and electrolyte deficits, and no potassium to exacerbate hyperkalemia.[4] However, it is important to remember that patients with significant hyponatremia can suffer severe neurologic consequences if their serum sodium concentration is raised too rapidly; such complications have been reported in dogs treated for hypoadrenocorticism[37,38] (see Chapter 54, Sodium Disorders). Because of the risks of rapidly increasing serum sodium concentration, a more appropriate therapy may be a balanced electrolyte solution with a lower sodium concentration (130 to 140 mEq/L), even though these solutions have 4 or 5 mEq potassium per liter. Restoration of effective circulating volume and resultant increase in glomerular filtration rate alone will help generate a kaliuresis, even if the fluid administered has potassium in it. Such decisions must be made on an individual basis. Frequent serum electrolyte measurements and neurologic examinations will help guide therapy.

76.7.2 Initial Hormonal Replacement

After endogenous ACTH measurement and ACTH stimulation testing, mineralocorticoid treatment should begin promptly. Mineralocorticoid supplementation should be provided in the form of desoxycorticosterone pivalate at a dosage of 2.2 mg/kg IM or SC once every 25 days for the life of the patient.[4,39] Fludrocortisone can also be used, but it is available only in oral form and often is not tolerated during the initial crisis event because of GI disturbance. Glucocorticoid supplementation during the adrenal crisis is appropriate and may or may not be required long term. Hydrocortisone, prednisolone, and dexamethasone are all available in injectable form, and any is appropriate. Hydrocortisone is recommended at an initial dosage of 1.25 mg/kg IV once, and 0.5 to 1 mg/kg IV q6h on a tapering schedule. Prednisolone can be given at an initial dosage of 4 mg/kg IV followed by 2 to 4 mg/kg IV q8h on a tapering schedule. The initial dosage of dexamethasone is 0.5 mg/kg IV, with subsequent doses of 0.05 to 0.1 mg/kg q12h on a tapering schedule.[4]

76.7.3 Supportive Therapies

Other therapy includes supportive care measures. Hypoglycemia should be corrected as required. Patients with GI disturbance may be treated with gastric protectants, and those with protracted vomiting may require antiemetic therapy. Patients with abdominal pain may require analgesia. Opiate medications are suitable for this purpose. Nonsteroidal antiinflammatory drugs should be avoided in patients with GI disturbance or azotemia and as such are almost always contraindicated in the hypoadrenal crisis. Concurrent disease such as aspiration pneumonia or sepsis should be treated appropriately.

76.7.4 Timeline for Clinical Improvement

Cats respond to therapy more slowly than dogs. Although a clinical response can be seen within hours in the dog, it may take 3 to 5 days for cats to show significant clinical improvement.[4,11]

76.8 ASSOCIATED DISORDERS

There have been reports of dogs brought in with hypoadrenocorticism that were concurrently diagnosed with immune-mediated diseases, including hemolytic anemia,[1,40] hypothyroidism,[1,5,41] myasthenia gravis,[1] and keratoconjunctivitis sicca.[32] These findings may support an immune-mediated etiology for primary hypoaldosteronism in dogs.

Megaesophagus has been reported occasionally in dogs with uncontrolled hypoadrenocorticism.* The connection between the two problems is unclear. It has been reported in dogs with typical hypoadrenocorticism, as well as those deficient only in glucocorticoids. Megaesophagus resolves with treatment of the hypoadrenocorticism.

* References 1, 4, 5, 7, 42, 43.

76.9 PROGNOSIS

If animals survive the initial crisis, long-term prognosis for both dogs and cats with naturally occurring Addison disease is very good with appropriate, lifelong therapy. Patients with primary hypoadrenocorticism often can be controlled with mineralocorticoid therapy alone, although many require glucocorticoid supplementation as well. Remember that many patients with atypical primary hypoadrenocorticism (adrenal failure with normal electrolytes and normal pituitary function) will become mineralocorticoid deficient. These patients require frequent reexamination, electrolyte evaluation, and vigilant monitoring by the owner so that the development of a hypoaldosterone state does not lead to life-threatening crisis. Those with secondary hypoadrenocorticism are well controlled on lifelong glucocorticoid therapy.

76.10 SUGGESTED FURTHER READING*

ED Feldman, RW Nelson: Hypoadrenocorticism (Addison's disease). In ED Feldman, RW Nelson (Eds.): *Canine and feline endocrinology and reproduction*. 2004, Saunders, St Louis, *The most comprehensive review of hypoadrenocorticism in the dog and cat. Also a primary reference, including information about over 200 dogs and 8 cats seen at the University of California.*

SJ Lifton, LG King, CA Zerbe: Glucocorticoid deficient hypoadrenocorticism in dogs: 18 cases (1986-1995). *J Am Vet Med Assoc*. **209**, 1996, 2076, *A retrospective study, the largest report of atypical primary hypoadrenocorticism in dogs. Characterizes the natural course of glucocorticoid deficiency, including progression of some dogs to a typical primary hypoadrenal state and concurrent disease including megaesophagus and immune-mediated disease in a few patients.*

ME Peterson, JM Feinman: Hypercalcemia associated with hypoadrenocorticism in 16 dogs. *J Am Vet Med Assoc*. **181**, 1982, 802, *A retrospective study that found hypercalcemia in 28% of dogs with hypoadrenocorticism over a 3-year period; etiology of hypercalcemia in Addison's disease unknown.*

ME Peterson, PP Kintzer, PH Kass: Pretreatment clinical and laboratory findings in dogs with hypoadrenocorticism: 225 cases (1979-1993). *J Am Vet Med Assoc*. **208**, 1996, 85, *The largest single study on hypoadrenocorticism in the dog; a retrospective study that evaluates breed predispositions, most common clinical pictures and laboratory findings, and clinical course of canine Addison's disease.*

* See the CD-ROM for a complete list of references

77 Chapter 77 Approach to Poisoning and Drug Overdose

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77.1 KEY POINTS

- The initial approach to the poisoned patient includes major organ system assessment and stabilization.
- Gastric evacuation can be achieved by induction of emesis, gastric lavage, or whole bowel irrigation.
- Activated charcoal is an adsorbent that binds toxins and facilitates excretion through the gastrointestinal (GI) tract.
- Cathartics often are used in combination with activated charcoal and decrease the absorption of toxins by shortening GI transit time.
- Other methods exist to enhance elimination of toxins but are not widely recommended because of their potential harmful effects or limited availability.

77.2 INTRODUCTION

Most animals with suspected poisoning or drug overdose may be treated successfully by adhering to general principles for assessment and decontamination. Initially, a brief medical history should be obtained from the owner with questions focusing on the suspected toxic agent, amount and time of ingestion, clinical signs noted, any preexisting medical conditions, and current medications. A more extensive history can be taken following triage and initial interventions.

Immediate assessment of the patient should be performed to evaluate vital signs and major body systems. Appropriate therapy should be initiated to stabilize the cardiovascular, respiratory, and neurologic systems. In the event of a witnessed ingestion, it may be appropriate to administer an antidote immediately. However, in many cases an antidote does not exist or the exact toxic agent is not known. Therefore, when treating the poisoned patient, decontamination often becomes the most effective means of therapy. Depending on the route of exposure, several methods of decontamination may be used to eliminate the toxin and prevent continued absorption. Further symptomatic and supportive care should be tailored to the needs of the individual patient.

77.3 OCULAR DECONTAMINATION

Ocular exposure to toxic substances can damage the corneal surfaces, conjunctiva, and other external tissues. These insults may result in local irritation or permanent corneal damage and blindness. Potential irritants include acids, alkalis, organic solvents, alcohols, and detergents. Acids and alkalis tend to have the most severe effects because progressive damage may occur for some time after initial contact.

With any ocular exposure, the pet owner should immediately perform copious irrigation of the eye. Irrigation solutions that may be used include tepid tap water, saline, or distilled water. Contact lens solutions should be avoided, because they may contain agents that cause further irritation. The eye should be rinsed for 20 to 30 minutes with the patient positioned such that the eye is flushed medially to laterally to prevent contamination of the other eye. Once the eyes have been flushed, the patient should be taken to a veterinarian or veterinary ophthalmologist for further evaluation.

77.4 DERMAL DECONTAMINATION

Exposure of the skin to toxic agents may cause local effects such as irritation and allergic dermatitis, or systemic effects if the toxin is absorbed. Although the epidermal layer is relatively impermeable to water-soluble substances, lipophilic agents or those containing surfactants are more readily absorbed. As with ocular exposure, rinsing or bathing the animal with mild dish soap is the standard method of decontamination for most dermal toxin exposures. However, care should be taken in cases of debilitated or intolerant patients, because bathing may exacerbate their preexisting conditions. Automatic dishwashing detergents and insecticidal shampoos should be avoided. The animal may need repeated baths to remove the toxin completely, and thorough rinsing should be performed to remove any remaining soap. During the bathing process, protective garments and rubber gloves should be worn to prevent human exposure to the toxic agent. After bathing, the animal should be thoroughly towel dried to prevent hypothermia.

77.5 GASTROINTESTINAL DECONTAMINATION

Gastrointestinal (GI) decontamination is used extensively in human and veterinary patients to limit exposure to ingested toxins and traditionally has consisted of gastric emptying followed by the administration of agents to hasten toxin elimination. Methods of gastric evacuation include emesis induction, gastric lavage, and whole bowel irrigation. Following gastric evacuation, activated charcoal may be administered to adsorb residual toxin. Cathartics frequently are used in conjunction with activated charcoal to shorten GI transit time and hasten elimination of ingested toxins.

77.5.1 Gastric Evacuation

77.5.1.1 Emesis

Emetics act either locally to cause gastric irritation or centrally at the chemoreceptor trigger zone to induce vomiting. A number of factors should be considered before inducing emesis including time of ingestion, agent ingested, and clinical status of the patient. Most emetics are effective only if given within 1 to 2 hours of ingestion, and induction of emesis does not eliminate the need for additional therapies, because emetics are successful at retrieving only a fraction of the gastric contents.[1] Emesis is contraindicated with ingestion of petroleum distillates, acids, and alkalis because of the risk of aspiration and chemical burns to the esophagus. Emesis should not be induced in animals with altered mentation or seizures because of the possibility of aspiration, in animals that are already vomiting, and in animals with preexisting health conditions such as significant cardiac disease, epilepsy, or recent abdominal surgery.

Three-percent hydrogen peroxide administered orally is used frequently to induce vomiting in cats and dogs. Because of its availability and low cost, hydrogen peroxide is often recommended to pet owners for use at home to promote rapid removal of ingested toxins. The dosage is 1 to 2 ml/kg, administered with a syringe or turkey baster.[2] Administration of hydrogen peroxide results in vomiting by triggering gastric irritation and is usually effective within minutes. The dose may be repeated once if emesis is not achieved. The use of more concentrated or higher doses of hydrogen peroxide is not advised, because it may lead to severe vomiting, mucosal irritation or ulceration, and salivation.

Apomorphine hydrochloride is a synthetic opiate that stimulates dopamine receptors in the chemoreceptor trigger zone to induce vomiting.[3] Apomorphine is considered by many veterinarians to be the emetic of choice in dogs, but its use in cats is unreliable. The recommended dosage in dogs is 0.03 mg/kg IV and 0.04 mg/kg IM.[2] Apomorphine may also be administered conjunctivally by crushing a portion of a tablet and dissolving it in a few drops of water. The conjunctival sac is then rinsed after emesis has occurred to prevent ongoing vomiting.[2] Adverse effects associated with apomorphine include protracted vomiting, restlessness, excitement, and central nervous system (CNS) depression. Naloxone may be used to the reverse the central nervous system depression but does not inhibit the emetic effects.[3]

Another emetic that can be used is xylazine hydrochloride, an α_2-adrenergic agonist. The recommended dosage for emesis in cats is 0.44 to 1.1 mg/kg IM or SC.[4] Adverse effects include sedation, bradycardia, arrhythmias, and muscle tremors. Once emesis has been achieved, the effects of the drug can be reversed with yohimbine hydrochloride at a dosage of 0.25 to 0.5 mg/kg IM.[4] Xylazine does not reliably produce emesis in dogs.

Syrup of ipecac is a nonprescription emetic that has been used in animals and is considered the emetic of choice in human patients. Ipecac is prepared from the roots of certain plants and contains two pharmacologically active compounds, the alkaloids emetine and cephaeline.[5] Ipecac functions as a local gastric irritant and also stimulates the chemoreceptor trigger zone in the brain to induce vomiting. Four studies have been performed in dogs to determine the value of ipecac-induced emesis using various compounds as markers. When ipecac was administered within 30 minutes of dosing, recovery rates varied from 17.5% to 45.6%.[6-9] Syrup of ipecac has been used at dosages of 1 to 2.2 ml/kg in dogs[6] and 3.3 ml/kg diluted in an equal volume of water in cats.[10] Reported adverse effects in humans associated with ipecac include diarrhea, drowsiness, prolonged vomiting, and cardiotoxicity at high dosages.[11] Ipecac has been shown to critically delay the administration of activated charcoal in poisoned human patients, and it is therefore no longer routinely recommended in their treatment.[11-13] Safer and more reliable emetics are available in veterinary patients.

The administration of liquid dishwashing detergents and table salt (sodium chloride) or mechanical stimulation of the pharynx to induce emesis are also not recommended. Excessive quantities of salt may result in hypernatremia and seizures. Attempts by pet owners to “gag” their pets are unreliable and may be dangerous to both the patient and the pet owner.

77.5.1.2 Whole Bowel Irrigation

Whole bowel irrigation is a decontamination technique that cleanses the entire bowel through the enteral administration of large amounts of an osmotically balanced polyethylene glycol electrolyte solution. The solution often is administered through a nasogastric tube until the rectal effluent resembles the infusate. In humans this procedure is most often considered with toxic ingestions of sustained release or enteric-coated drugs, iron, and packets of illicit drugs.[14] A study evaluating whole bowel irrigation in six paraquat-poisoned dogs revealed a mean recovery rate of 68.9%, with total body clearance significantly greater in the bowel irrigation group when compared with the control group.[15] However, adverse effects were not evaluated, because all animals were euthanized at the end of the study. This procedure is contraindicated in patients with possible bowel perforation, GI hemorrhage or obstruction, ileus, compromised airway, intractable vomiting, and hemodynamic instability. Reported complications in humans include nausea, vomiting, abdominal cramping, and bloating.[14] The clinical usefulness of whole bowel irrigation in veterinary patients is not known.

77.5.1.3 Gastric Lavage

Gastric lavage is the administration and evacuation of small volumes of liquid through an orogastric tube to remove toxic substances within the stomach. This procedure may be indicated when emesis has failed, when emesis is contraindicated (depressed mental state, loss of gag reflex), or when administration of charcoal is critical and emesis would delay its administration. Contraindications to gastric lavage include ingestion of hydrocarbons because of high aspiration potential, ingestion of corrosive substances, and risk of hemorrhage or GI perforation resulting from pathology or recent surgery. As with induction of emesis, the effectiveness of this procedure is dependent on the time of ingestion and is likely to be most effective within the first 1 to 2 hours postintoxication.[6-8]

In the conscious animal, gastric lavage is performed after induction of general anesthesia with the patient intubated to prevent aspiration. The cuff of the endotracheal tube should be assessed before initiation of gastric lavage to ensure a snug fit. The patient is positioned in lateral recumbency with the head lower than the thorax. A large-bore gastric tube with a fenestrated end is placed alongside the patient and the distance measured from the tip of the nose to the last rib. The fenestrated end of the tube may then be lubricated and gently passed down the esophagus into the stomach to the marked distance on the tube. Tube placement may be confirmed by aspiration of gastric contents, air insufflation with a stethoscope placed over the stomach, or by radiographic confirmation. Warm water or saline is infused into the tube, with approximately 5 to 10 ml/kg per cycle to moderately distend the stomach. The fluid is then allowed to drain from the tube via gravity flow. The procedure is repeated until clear fluid is returned. Activated charcoal may then be administered through the tube. The end of the tube should be occluded before removal to prevent spillage of tube contents into the pharynx.

In human patients, gastric lavage is not recommended in the routine treatment of poisoned patients because of the lack of evidence that it improves clinical outcome and because of the potential for increased morbidity.[16] Three studies performed in animals have similarly failed to demonstrate substantial drug recovery. If gastric lavage was performed within 15 to 20 minutes of ingestion, the mean recovery of the marker was 29%[8] and 38%.[6] When this procedure was performed after 60 minutes, mean recoveries were only 8.6%[7] and 13%.[6]

Several risks are associated with gastric lavage. Aspiration pneumonia is the most commonly reported complication and emphasizes the need for endotracheal intubation during the procedure. In humans, electrolyte imbalances such as hyponatremia have been reported, so it is recommended that pediatric patients receive normal or half-strength saline instead of tap water. Mechanical injury to the throat and esophagus may also occur, because the gastric tubes are often rigid. Hypoxia and hypercapnia have also been reported in human patients that have undergone this procedure.[16]

77.5.2 Adsorbents

77.5.2.1 Activated Charcoal

Activated charcoal is a carbonaceous compound that is produced by the pyrolysis of organic material such as wood pulp or coal. It is then activated by an oxidizing gas at high temperatures to break down the carbon into smaller granules with larger surface areas.[17] The larger surface area allows many binding sites for adsorption of toxic agents. Most activated charcoal compounds have a surface area of approximately 1000 m^2 per gram, but experimental charcoal preparations have been manufactured with surface areas of up to 3500 m^2.[18] Activated charcoal is available in the form of granules, tablets, capsules, or as a suspension. The suspension may also be obtained in combination with a cathartic such as sorbitol. In human patients the suspension is significantly more effective than the tablets or capsules.[19]

Activated charcoal does not adsorb every toxin effectively. Several factors may play a role, including temperature, pore size of the charcoal, surface area of the charcoal, solubility of the toxin, ionization of the toxin, pH, and presence of other gastric contents.[20] Activated charcoal is not effective with compounds such as alcohols, ferrous sulfate, caustic alkalis, nitrates, petroleum distillates, or mineral acids. However, because many toxins are effectively bound to charcoal, it should be administered when there is a high suspicion of significant unknown toxin ingestion. The recommended dosage of activated charcoal is 1 to 4 g/kg.[2] Pets exhibiting no clinical signs may drink the charcoal freely. A small amount of food may be added to the solution to enhance palatability; however, mineral oils, milk, and ice cream have been shown to decrease charcoal's adsorptivity.[21] Charcoal may be administered via syringe, but there is a risk of aspiration with this technique and more of the charcoal is likely to be lost during administration. In animals exhibiting clinical signs, charcoal may be administered through an orogastric tube with a cuffed endotracheal tube in place to protect against aspiration. Another useful technique, especially in cats, is administration of the charcoal through a nasogastric tube. Tube placement should always be confirmed before administration.

As with most decontamination procedures, activated charcoal is most effective if given soon after toxin ingestion. In the human literature, it has been shown that administration is most effective within 1 hour of toxin ingestion. However, the potential for benefit beyond 1 hour cannot be excluded.[20,22-25] Multiple doses of activated charcoal may be appropriate when treating for toxins that undergo enterohepatic circulation or with drugs that diffuse into the intestinal tract from the systemic circulation down their concentration gradients. In these situations charcoal is repeated every 4 to 8 hours and may be beneficial for several days. In human patients, substantial decreases in serum half-life with the use of multidose activated charcoal have been reported for theophylline, phenobarbital, digitoxin, dapsone, and antidepressants.[26]

When other methods of decontamination such as emesis induction or gastric lavage are employed, charcoal administration may be delayed. Human studies have questioned the need for gastric emptying procedures before administration of activated charcoal, and several have shown that charcoal alone is as effective as gastric emptying and charcoal combined.[12,13,27] Further studies are needed in animals to determine the effectiveness of charcoal alone in the treatment of acute poisoning.

Activated charcoal should not be administered following hydrocarbon ingestion or when the airway is unprotected because of the potential for aspiration. Patients who are at risk of GI hemorrhage or perforation due to pathology or recent surgery may be further compromised by charcoal administration. One of the most commonly reported adverse effects associated with charcoal administration is vomiting, especially when charcoal is administered in large volumes or with sorbitol-containing preparations. Aspiration is another potential complication. Intratracheal instillation of charcoal may result in significant increases in pulmonary microvascular permeability, contributing to lung edema formation and pulmonary compromise.[28]

77.5.3 Cathartics

Cathartics decrease the absorption of substances by accelerating their expulsion from the GI tract. Cathartics often are administered with charcoal to hasten toxin elimination from the GI tract before absorption. If multiple doses of activated charcoal are given, a cathartic should be used only with the first dose of charcoal to prevent diarrhea and dehydration. Cathartics are contraindicated in cases of recent abdominal trauma, recent bowel surgery, intestinal obstruction or perforation, or with ingestion of a corrosive substance.[29]

The two types of cathartics used in poisoned patients are saccharide cathartics (sorbitol) and saline cathartics (magnesium citrate, magnesium sulfate, and sodium sulfate). Sorbitol is a nonabsorbable sugar that is metabolized to fructose following oral administration. Fructose then acts as an osmotic agent. Sorbitol is often combined with charcoal in a commercially available product, because it improves the palatability of charcoal and helps mask the gritty texture. A comparison of sorbitol, magnesium sulfate, and magnesium citrate in pediatric patients revealed that sorbitol produced a shorter time to first stool and more stools than magnesium citrate and magnesium sulfate.[30] Sorbitol use has been associated with severe dehydration and hypernatremia in humans, so careful monitoring of the patient's hydration status is recommended.[31]

Magnesium sulfate and sodium sulfate salts are saline laxatives. The hyperosmotic effects of the poorly absorbed magnesium or phosphate ions cause water retention within the intestinal lumen, stimulating stretch receptors and enhancing peristalsis. Dosages range from 5 to 25 g PO in the dog and 2 to 5 g PO in the cat.[2] These agents may be combined with charcoal suspensions or given soon after charcoal administration. It is estimated that up to 20% of the phosphate and 30% of the magnesium in these solutions may be absorbed.[32] Sodium-containing solutions should be avoided in patients with congestive heart failure, renal disease, or severe dehydration. Magnesium-based cathartics should be avoided in patients with renal insufficiency or prolonged GI transit time, because resultant hypermagnesemia may cause muscle weakness, electrocardiographic changes, and CNS dysfunction.

77.6 ENHANCED ELIMINATION

Other methods that have been used to enhance the elimination of certain toxins and drugs from the body include forced diuresis, ion trapping, hemodialysis, and hemoperfusion. Forced diuresis using large volumes of intravenous fluids may be effective for toxins that are eliminated primarily through the kidneys. However, this treatment carries some risk of volume overload with resulting pulmonary and cerebral edema. Therefore as a general principle this technique should be avoided unless specifically indicated by the nature of the toxin ingested. Manipulation of urine pH with alkalinizing or acidifying agents has been proposed to trap substances in the ionized form and enhance elimination. However, the agents used to accomplish these goals may induce a systemic alkalosis or acidosis that may be more detrimental to the patient than the toxin itself. Therefore this therapy as a general treatment should be avoided. Hemodialysis and hemoperfusion are techniques that allow blood to be removed from the body, filtered through a membrane or an adsorbent material, and then returned to the patient. These techniques are highly effective for certain toxins, but are unfortunately not widely available in veterinary practice (see Chapter 137, Hemodialysis and Peritoneal Dialysis).

77.7 SUPPORTIVE CARE

The goals of therapy in any toxicologic emergency should include prevention of further toxin absorption, administration of appropriate antidotes when applicable, and supportive care. Many toxins or their metabolic by-products have the potential to cause secondary organ damage beyond the initial insult. Therefore, in addition to general decontamination procedures and specific antidotes, intoxicated patients may require further clinical sign–targeted treatments and supportive care. These include maintenance of respiratory and cardiovascular function, control of acid-base disorders, maintenance of body temperature, and control of CNS disorders. Regardless of the toxin ingested, a problem-oriented approach should always be employed to determine the most effective and appropriate therapies for each individual patient.

77.8 SUGGESTED FURTHER READING*

VR Beasley, DC Dorman: Management of toxicoses. *Vet Clin North Am Small Anim Pract*. **20**, 1990, 307, *A review article discussing the general approach to toxicities in small animals, including patient assessment and methods of decontamination*.

D Teshima, A Suzuki, K Otsubo, et al.: Efficacy of emetic and United States Pharmacopoeia ipecac syrup in prevention of drug absorption. *Chem Pharm Bull*. **38**, 1990, 2242, *Study that evaluates the efficacy of ipecac-induced emesis in fasting dogs using several drugs as markers*.

JA Vale, K Kulig: American Academy of Clinical Toxicology, European Association of Poison Control Centres and Clinical Toxicologists: Position paper: gastric lavage. *J Toxicol Clin Toxicol*. **42**, 2004, 933, *Study that reviews human and animal studies on gastric lavage, discusses risks of the procedure, and makes recommendations for its use in the intoxicated patient*.

* See the CD-Rom for a complete list of references

78 Chapter 78 Ethylene Glycol

Christopher Rollings, DVM, DACVIM

78.1 KEY POINTS

- Ethylene glycol (EG) is a relatively common and potentially fatal intoxicant in small animals.
- The metabolites of EG are responsible for most of the systemic toxicity.
- Decreased mentation and an elevated osmolal gap are two of the earlier findings seen after exposure. Later laboratory findings include renal azotemia, ionized hypocalcemia, and severe metabolic acidosis.
- Both quantitative and semiquantitative methodologies are available for EG testing.
- Treatment is based on appropriate supportive care, alcohol dehydrogenase inhibition, and/or dialytic removal of the toxin and its metabolites.
- The prognosis is highly dependent on time from exposure to diagnosis and treatment.

78.2 INTRODUCTION

Ethylene glycol (EG) is a clear, odorless compound that, because of its palatability, is occasionally ingested by both dogs and cats, with severe and potentially fatal consequences. EG is found in antifreeze (95% solution), windshield de-icing agents, and some industrial solvents (detergents, photographic developing solutions, brake fluid, motor oil, paints, wood stains, and polishes). Data regarding the incidence of this intoxication in veterinary medicine are sparse, but EG was the second most common intoxication at the Colorado State University veterinary teaching hospital between 1979 and 1986. The reported mortality rate ranges from 59% to 70% in dogs and is primarily dependent on the time that elapses between ingestion of the toxin and institution of treatment. Cats and humans are the species considered most susceptible to EG intoxication. The minimum lethal dosage in dogs is reported as 4.4 to 6.6 ml/kg but is as low as 1.5 ml/kg in cats.[1]

78.3 METABOLISM

EG is absorbed rapidly from the gastrointestinal (GI) tract (although food slows its absorption time) and is distributed throughout all body tissues. Some of the toxin is eliminated unmetabolized in the urine. Serum concentrations rise rapidly by 1 hour and, in dogs and cats, are typically highest by 3 hours after ingestion. Levels are typically elevated for at least 12 hours but may be undetectable by 48 hours.[1]

Knowledge of the metabolism of EG is paramount to understanding its toxicity and treatment (Figure 78-1). Metabolism is accomplished primarily in the liver, with a small contribution from the kidneys and stomach. Alcohol dehydrogenase (ADH), an important therapeutic target, converts EG to glycoaldehyde and organic acids. The glycoaldehyde is then converted to glycolate (glycolic acid [GA]), then glyoxylate (also known as glyoxylic acid). Because the metabolism of GA is rate limiting, this metabolite achieves much higher concentrations in the blood than any of the others. Glyoxylate is converted primarily to oxalate, but additional end products include glycine, formic acid, hippuric acid, oxalomalic acid, and benzoic acid. The oxalate formed from glyoxylate combines with calcium to form the characteristic calcium oxalate crystals that are deposited throughout the body, but primarily in the kidneys.[1,3]

78.4 TOXICITY AND SYSTEMIC EFFECTS

Compared with its metabolites, EG is relatively nontoxic, but it is a potent central nervous system (CNS) depressant and GI irritant. Its metabolites are highly toxic and have a myriad of deleterious systemic sequelae. Glyoxylate and glycoaldehyde are considered the most toxic of the metabolites on a per weight basis. However, because of its longer half-life and greater systemic accumulation, GA is thought to be the major mediator of in vivo toxicity.[1]

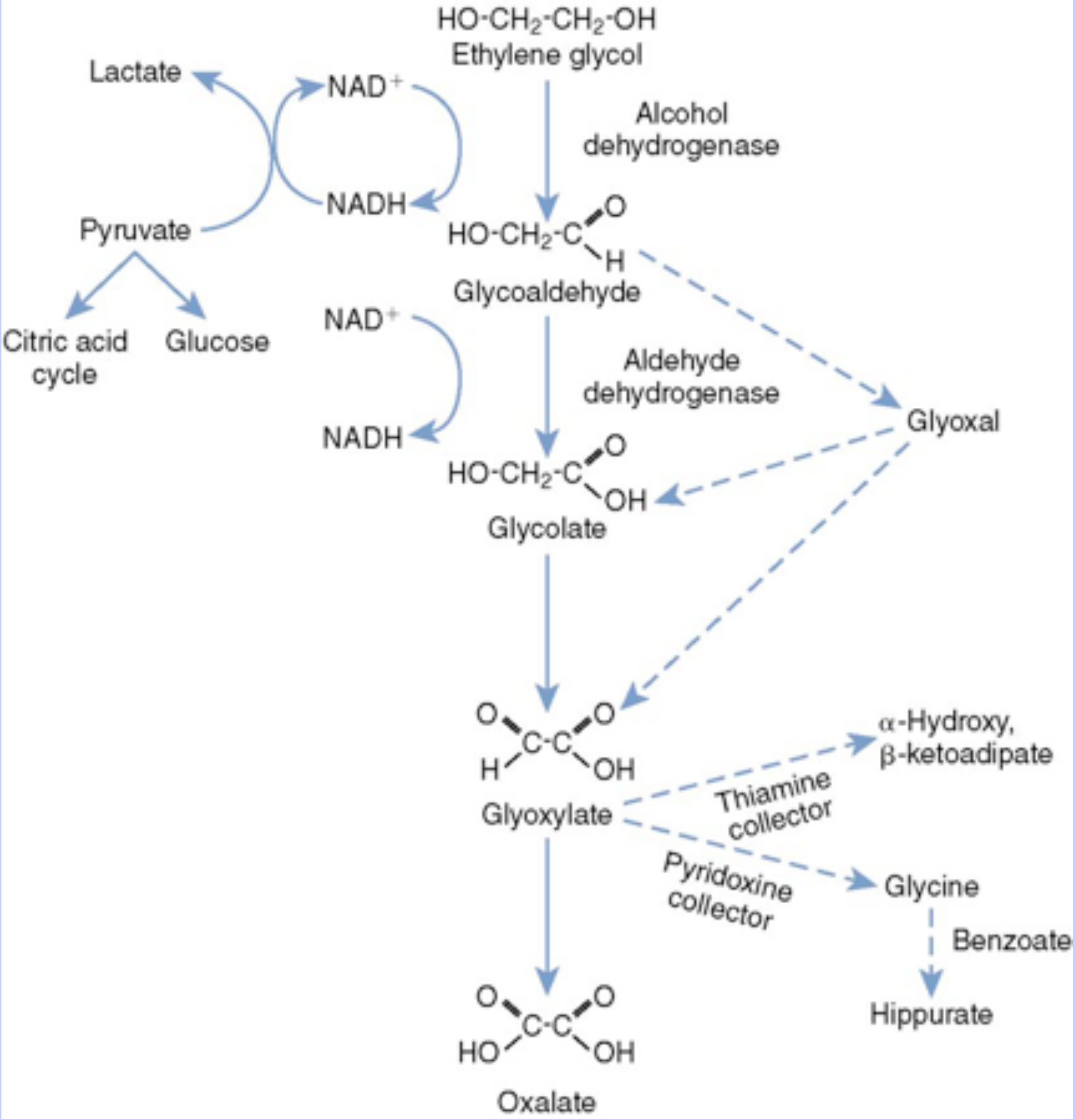
CNS depression can occur within 30 minutes of EG ingestion and typically manifests as depression, incoordination, and ataxia. With more severe intoxications, paresis, somnolence, seizures, and coma can be seen. It is extremely important to associate these clinical signs with EG toxicity because these are some of the earliest manifestations of intoxication, and thus recognition can lead to early and effective treatment. The CNS signs may abate 12 hours post ingestion in dogs, and patients often appear to have "recovered" for a brief time. The CNS effects are thought to result from a combination of direct effects from aldehyde metabolites, hyperosmolality, and metabolic acidosis. Glycoaldehyde adversely affects respiration, glucose, CNS amine concentrations, and serotonin metabolism. For this reason, CNS toxicity correlates better with GA than EG concentrations.[1,5]

GI manifestations are highly nonspecific. Vomiting can occur immediately post ingestion from direct gastric mucosal irritation. It can also be seen as serum osmolality rises, thus stimulating the chemoreceptor trigger zone. Deposits of calcium oxalate and focal bleeding have been found in the stomach at necropsy. Severe GI disturbance is often a common late sequela, as acute renal failure (ARF) progresses to uremia.[1]

Cardiorespiratory effects are a much less prominent manifestation of EG poisoning in dogs and cats compared with humans. Tachycardia and tachypnea are seen more commonly in dogs than in cats. Hypocalcemia and metabolic acidosis can both lead to arrhythmogenesis and decreased inotropy. Myocardial calcium oxalate deposition is occasionally documented during necropsy.[1,3]

ARF is the most commonly associated and best documented systemic manifestation of EG intoxication in small animal medicine. ARF typically occurs 24 to 72 hours after ingestion in dogs but can occur as early as 12 hours after ingestion in cats. Unlike with some other nephrotoxicants such as nonsteroidal antiinflammatory drugs and aminoglycosides, EG is often associated with oliguric or anuric ARF. Mechanisms of nephrotoxicity are still incompletely understood. Calcium oxalate crystal deposition within the tubules and proximal tubular epithelium plays a role, but in humans the degree of renal damage is not correlated with the degree of crystal formation.

Figure 78-1 The metabolic pathway of ethylene glycol.



Direct renal tubular epithelial cytotoxicity from EG metabolites likely plays a significant role in the acute tubular necrosis (ATN). Glyoxylate and glycoaldehyde are highly nephrotoxic in vitro; however, GA is thought to be one of the main mediators of acute tubular necrosis that is seen in clinical cases. In humans, GA concentrations correlate with progression to ARF, and levels greater than 10 mmol/L are highly predictive of ARF. Duration of exposure to cytotoxic metabolites is thought to influence the degree of renal injury as well. Polyuria and polydipsia (PU/PD) can be marked in dogs, often develop shortly after EG ingestion, and are secondary to an osmotic diuresis.[1,3,5]

78.5 DIAGNOSIS

As will be discussed in the next section, early treatment of EG intoxication is extremely important to achieve a successful clinical outcome. Early diagnosis is therefore key. Clinical signs are dose dependent and related to those caused by unmetabolized EG, followed by those caused by the toxic metabolites. Initial clinical signs are often apparent 30 minutes after EG ingestion and include nausea and vomiting, CNS depression, ataxia, decreased proprioception, lower motor neuron signs to the limbs, muscle fasciculations, hypothermia, and polyuria and polydipsia. The CNS changes typically abate after 12 hours in dogs, but cats often remain severely depressed. Clinical signs of ARF (24 to 72 hours in dogs and 12 to 24 hours in cats) may include coma and depression, anorexia, vomiting, seizures, ptyalism, and oral ulcerations. Anuria is commonly seen 72 to 96 hours after ingestion, and the kidneys are often painful and swollen upon palpation in cats.

78.5.1 Box 78-1 Calculation of Osmolal Gap

OG = Measured OG – Calculated OG

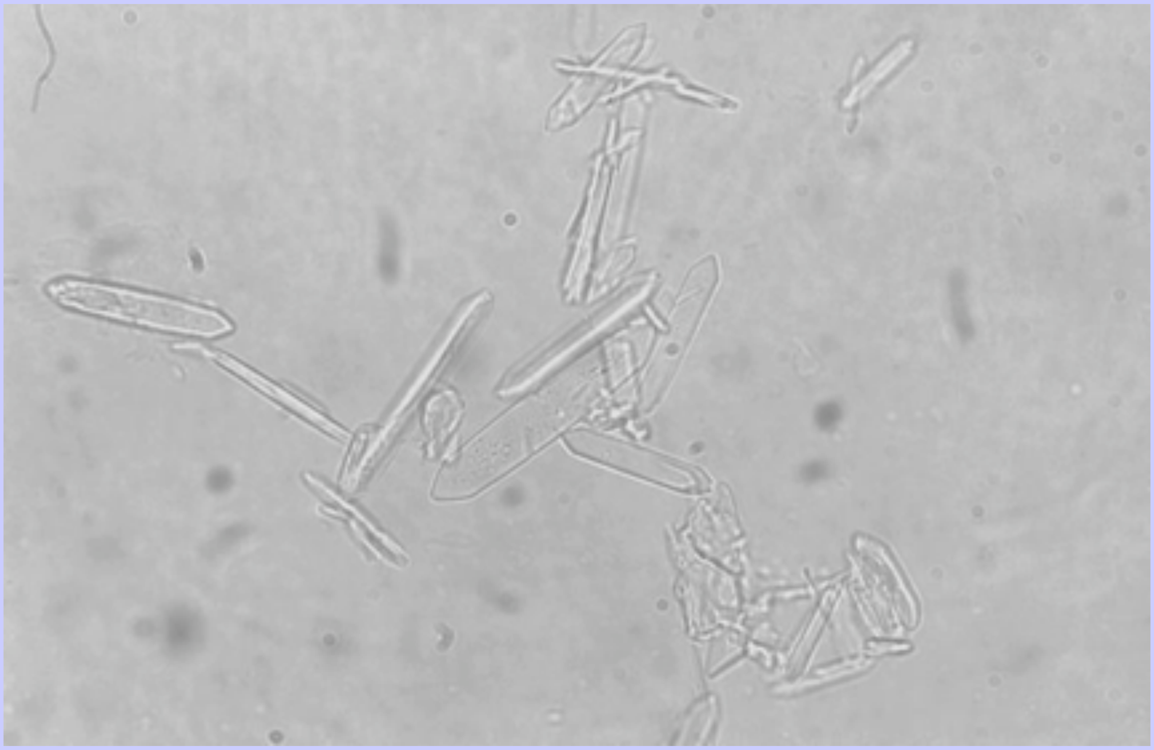
Calculated OG = 2(Na + K) + (BUN ÷ 2.8) + (Glucose ÷ 18)

BUN, Blood urea nitrogen; *K,* potassium; *Na,* sodium; *OG,* osmolal gap.

The first clinicopathologic finding seen in patients with EG ingestion is a rise in the osmolal gap (OG) (Box 78-1). This can occur as early as 1 hour after ingestion in cats and dogs and typically peaks by 6 hours in dogs. The OG remains elevated for approximately 18 hours after ingestion of EG. The OG correlates well with EG concentration in both humans and dogs, and in human intoxications the deviation from a particular laboratory's “normal” OG (typically around 10 mOsm/kg H_2O; up to 150 mOsm/kg with EG toxicity) can be multiplied by 6.2 to estimate EG concentration in mg/dl. Data from dogs again show a high correlation between OG and EG concentrations, but this formula appears to be less reliable in this species. Serum osmolality should be measured by freezing point depression to accurately calculate the OG.[1,3-6]

A high anion gap (AGAP) and a normochloremic metabolic acidosis develops within 3 hours of ingestion in dogs and cats, peaks at 6 hours, and may last for up to 48 hours. This metabolic acidosis may be quite severe, with extremely low serum bicarbonate concentrations. In humans, most of the AGAP (greater than 95%) is attributable to GA accumulation, an extremely important finding because this represents irreversible metabolism of EG and warrants that makes many treatment strategies less effective. GA also has been shown to correlate with AGAP in dogs, although not as closely as is seen in humans.[1,3,6]

Figure 78-2 Urine sediment with calcium oxalate monohydrate crystals.



Numerous biochemical abnormalities can be seen in patients with EG intoxication. Hyperphosphatemia and azotemia are observed with progression to ARF. The former can also be seen shortly after ingestion due to phosphorus-containing rust inhibitors found in many antifreeze preparations. Hyperkalemia is seen during progression to oliguria/anuria and is exacerbated by metabolic acidosis. Ionized hypocalcemia is seen in over 50% of intoxicated dogs and cats. This is thought to be secondary to chelation with oxalic acid and the subsequent development of calcium oxalate crystals. Clinical signs of hypocalcemia are uncommonly observed. Hyperglycemia is seen in over 70% of intoxicated cats and dogs and is thought to result from aldehyde-induced inhibition of glucose metabolism, increased epinephrine and endogenous cortisol, and uremia.[1]

Calcium oxalate crystalluria can be seen within 3 hours of EG ingestion in cats and within 4 to 6 hours in dogs. Both monohydrate and dihydrate crystals can be seen, although the former are considered more specific (although still not 100%) for EG poisoning in small animals. The monohydrate crystals appear as clear, six-sided prisms of variable sizes on urine sediment examination (Figure 78-2). Duration of crystalluria is highly variable but can be days in animals that develop ARF. Isosthenuria is seen even before development of ARF (often within 3 hours) resulting from the osmotic diuresis and polydipsia and then persists in the later stages of toxicosis as renal concentrating mechanisms become dysfunctional. Additional urine abnormalities may include glucosuria, hematuria, proteinuria, pyuria, and granular and cellular casts. Urine can also be evaluated with the presence of a Wood's lamp, because the fluorescein stain found in many antifreeze preparations will fluoresce up to 6 hours after ingestion of the toxin.[1,3] Examination of the oral cavity, face, paws, and vomitus may also reveal fluorescence.

Serum EG concentrations typically peak 1 to 6 hours after ingestion of the toxin, and EG is rarely present in the blood or urine after 48 to 72 hours. Definitive diagnosis and quantification of EG levels can be performed using gas chromatography. This test is expensive and not readily available. In veterinary medicine, a glycol test kit is also available that detects EG concentrations of greater than 50 mg/dl. This test kit is not considered sensitive enough for reliable use in cats. Propylene glycol and glycerol can cause false-positive results with both of the previously mentioned testing methodologies.[1,3] Severe elevations of lactate dehydrogenase or lactic acid may cause false-positive results for EG when enzymatic methods of testing are performed.

Renal ultrasound, although not pathognomonic for EG intoxication, can be highly suggestive of EG nephrotoxicity. Affected kidneys are often markedly hyperechoic. Enhanced echogenicity of the cortical and medullary regions with hypoechoic corticomedullary and central medullary tissue is referred to as a *halo sign* and has been associated with the development of anuria. Renal ultrasonographic changes can occur as early as 4 to 6 hours after EG ingestion.[1] Histopathologic examination of kidney tissue typically reveals calcium oxalate crystals within the renal tubules in animals suffering form EG-induced renal failure.

78.6 TREATMENT

Because EG is absorbed rapidly by the GI tract, induction of emesis and/or gastric lavage is likely only of benefit within 2 hours of ingestion. Caution must be exercised to prevent aspiration pneumonia if emesis is induced. Activated charcoal is of questionable benefit in cases of EG ingestion, because very little is adsorbed. Its use is not advocated in human intoxications in the absence of co-ingested toxins.[1,3] Therapy for EG toxicity is therefore primarily based on increasing excretion and preventing metabolism.

As discussed at length previously, EG metabolites are responsible for systemic toxicity and, with the exception of CNS depression and direct gastric irritation, not EG itself. ADH is responsible for the first step in EG metabolism/oxidation and therefore represents an extremely useful therapeutic target. Because ADH inhibition has no effect on already-metabolized EG (e.g., from glycoaldehyde forward in the metabolic pathway), it is only effective when given very soon after ingestion. In small animal EG intoxications, ADH inhibition is most effective within 6 to 8 hours after exposure (slightly shorter therapeutic window in cats compared with dogs). Indications for an antidote in human medicine include EG concentration greater than 20 mg/dl, documented ingestion and OG greater than 10 mOsm/L, and strong clinical suspicion of EG ingestion with two or more of the following: pH less than 7.3, bicarbonate less than 20 mEq/L, OG greater than 10 mOsm/L, and calcium oxalate crystalluria.[1,3]

Ethanol was the first compound used to block EG metabolism and is still commonly used in small animals. Ethanol has a higher affinity for ADH than EG. Two protocols are used in veterinary medicine (Box 78-2). The intermittent protocol is associated with greater CNS depression than the continuous protocol. The CNS depression from ethanol treatment can be severe, especially in cats, and respiratory arrest is a rare sequela. Consequently, intensive monitoring is extremely important when using an ethanol protocol. It is important to remember that ethanol exacerbates the hyperosmolality and osmotic diuresis associated with EG ingestion. Additionally, ethanol exacerbates the metabolic acidosis by enhancing the formation of lactate from pyruvate. The target blood ethanol concentration in human medicine is 100 mg/dl, although approximately half this level appears to be effective in dogs and cats. Ethanol infusions have been associated with hypoglycemia in humans, presumably because it is metabolized to acetaldehyde, which impairs gluconeogenesis. Blood glucose concentrations should therefore be monitored during ethanol therapy.[1,3,4]

78.6.1 Box 78-2 Suggested Protocols for Specific Therapy for Ethylene Glycol Intoxication in Dogs and Cats

78.6.1.1 Ethanol*

Dogs

- 20% ethanol
  - 5.5 ml/kg IV q4h for 5 treatments, then q6h for 4 treatments
  - ***or***
  - Same total dose given CRI
- 30% ethanol (low dose protocol)
  - 1.31 ml/kg slow IV bolus, followed by 0.42 ml/kg/hr for 48 hours
  - ***or***
  - 300 mg/kg slow IV bolus, followed by 100 mg/kg/hr CRI

Cats

- 20% ethanol
  - 5.0 ml/kg IV q6h for 5 treatments, then q8h for 4 treatments

78.6.1.2 4-Methylpyrazole (50 mg/ml)

Dogs

- Initial loading dose: 20 mg/kg IV†
- At 12 hours: 15 mg/kg IV

At 24 hours: 15 mg/kg IV

At 36 hours: 6 mg/kg IV‡

CRI, Constant rate infusion; *IV,* intravenously.

* 60% Ethanol (100 proof) contains 393 mg ethanol/ml.

† Slow IV infusion over 15 to 20 minutes.

‡ If the dog is not recovered and there is suspicion for remaining unmetabolized ethylene glycol, continue to administer 5 mg/kg IV q12h.

4-Methyl-1 H-pyrazole (4-MP, fomepizole) represents an important therapeutic advance in ADH inhibition. 4-MP is a strong, competitive inhibitor of ADH, with greater affinity for ADH than ethanol. Unlike ethanol, it is not associated with CNS depression, hyperosmolality, or osmotic diuresis and therefore requires less intensive monitoring than the ethanol infusion protocols 4-MP has much more predictable pharmacokinetics than ethanol, another advantage of its use.

The recommended dosage of 4-MP in dogs is 20 mg/kg of body weight IV, followed by 15 mg/kg IV at 12 and 24 hours, and 5 mg/kg IV at 36 hours. Humans with EG toxicity that undergo hemodialysis are also treated with 1 to 1.5 mg/kg/hr of 4-MP, because the 4-MP is lost in the dialysate. Levels of 4-MP in the blood can be determined using high-performance liquid chromatography. The fomepizole protocol used for canine intoxications has proven ineffective for treatment of cats, and one study has shown that 6 times the given canine fomepizole concentration is required in cats to achieve an equivalent level of ADH inhibition. Preliminary work has shown that high-dosage fomepizole therapy is safe and more effective than the ethanol infusion protocol in cats, although heavy sedation is sometimes seen.[7] The cost of fomepizole may prove prohibitive in some animals.

1,3-Butanediol, which has a high affinity for ADH, has been used experimentally in dogs to treat EG intoxication. It does, however, contribute further to hyperosmolality, and metabolites of 1,3-butanediol may exacerbate the metabolic acidosis. Additional therapies that prevent metabolism of glyoxylic acid to nontoxic end products include thiamine and pyridoxine.

Hemodialysis, although not widely available in veterinary medicine, is an important treatment modality for animals with EG intoxication. Hemodialysis, unlike any other treatment option, removes not only EG but also its toxic metabolites from the circulation. In human medicine, EG concentrations of greater than 50 mg/dl were previously considered an indication for hemodialysis. With acceptance of 4-MP as an effective treatment, the paradigm has shifted to assessment of progression down the metabolic pathway when considering hemodialysis. GA concentration, which as discussed previously is highly associated with development of metabolic acidosis, is becoming accepted as a better marker of need for hemodialysis. Guidelines proposed for use of hemodialysis in human EG toxicosis include pH <7.25 to 7.3, renal failure unresponsive to conventional therapy, and GA concentration greater than 8.5 mmol/L. Although similar guidelines have not been established in veterinary medicine, both EG and GA are readily dialyzable in poisoned dogs.[3,6]

Supportive therapy is extremely important in achieving a successful outcome in animals with EG intoxication. Because both EG and ethanol are associated with significant osmotic diuresis, aggressive intravenous crystalloid support is critical to prevent dehydration, as well as to facilitate renal EG clearance and minimize tubular obstruction from crystal precipitation. Small animals that are not treated promptly with an antidote and that subsequently develop ARF frequently progress to oliguria and then anuria. It is therefore crucial to monitor urine output, body weight, electrolytes, kidney values, blood glucose concentration, acid-base status, and hematocrit/total solids several times daily to prevent potentially fatal overhydration and dangerous electrolyte abnormalities.

Small animals typically develop severe metabolic acidosis within hours of EG ingestion, and treatment with bicarbonate may be necessary. Bicarbonate therapy will exacerbate hypocalcemia, occasionally precipitating symptomatic ionized hypocalcemia.[1] Intoxicated animals are prone to hypothermia, and rectal temperature should be monitored frequently and heat support provided as needed. Additional supportive care for animals in renal failure can be found in Chapter 135, Acute Renal Failure. Details pertaining to diuretic and GI supportive care can be found in the section entitled Pharmacology, as well as Chapters 180 to 182, Diuretics, Gastrointestinal Protectants, and Antiemetics, respectively.

78.7 PROGNOSIS

The prognosis for dogs and cats suffering from EG toxicosis is highly dependent on the time from ingestion until either antidotal or dialytic therapy is instituted. The prognosis of dogs and cats treated with ethanol or 4-MP within 8 hours after ingestion is typically good, although individual differences in EG metabolism lead to some variability.

Because the metabolic acidosis is associated with metabolite accumulation, blood pH may prove to be a useful indicator of the short-term and long-term prognosis (as in human patients). The prognosis for small animals that have progressed to anuric ARF is grave, because these patients are typically unresponsive to treatment aimed at reestablishing urine output. Anuric dogs have been treated long term with hemodialysis, and 20% of these dogs 333
have recovered enough function to be taken off dialytic support and be maintained as patients with chronic renal 334
failure. This recovery takes weeks to months to occur. Both the incidence and degree of renal recovery appear to be much less in our small animal patients compared with what is seen in humans with EG-induced ARF.

78.8 SUGGESTED FURTHER READING*

DG Barceloux, EP Krenzelok, K Olson, W Watson: American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. Ad Hoc Committee. *J Toxicol Clin Toxicol*. **37**, 1999, 537, *One of the more practical articles on human EG intoxication but, as the title suggests, provides only cursory pathophysiologic explanation*.

HE Connally: In Ethylene glycol: A review and what's new, International Veterinary Emergency and Critical Care Symposium, September 7-11, 2005 2005, Georgia, Atlanta, *A very practical abstract that includes a protocol for fomepizole use in cats*.

AR Gaynor, N Dhupa: Acute ethylene glycol intoxication. *Part I, Compend Contin Educ Pract Vet*. **21**, 1999, 1014.

AR Gaynor, N Dhupa: Acute ethylene glycol intoxication. *Part II, Compend Contin Educ Pract Vet*. **21**, 1999, 1124, *Two-part excellent review articles on EG intoxication of dogs and cats. Very easy to read, excellent job of integrating metabolism and physiology with practical diagnosis and treatment information*.

D Jacobsen, KE McMartin: Antidotes for methanol and ethylene glycol poisoning. *J Toxicol Clin Toxicol*. **35**, 1997, 127, *A to-the-point synopsis of the diagnosis and treatment of EG intoxication in human medicine. A nice review article that is easy to read.*

WH Porter, BA Bush, AA Pappas, et al.: Ethylene glycol toxicity: the role of serum glycolic acid in hemodialysis. *J Toxicol Clin Toxicol*. **39**, 2001, 607, *A very interesting review article that shifts the paradigm of when to use hemodialysis away from focusing on EG concentrations to presence of toxic metabolites*.

* See the CD-ROM for a complete list of references

79 Chapter 79 Acetaminophen

Amy J. Alwood, DVM

79.1 KEY POINTS

- Acetaminophen toxicity from accidental exposure or deliberate administration in dogs and cats is the second most common cause of nonsteroidal antiinflammatory drug (NSAID) toxicity in small animals.
- Acetaminophen toxicity may result from dosages exceeding 75 mg/kg in the dog, although dosages as low as 10 mg/kg have been associated with toxicity in the cat.
- Toxicity from acetaminophen results when the metabolic pathways for glucuronidation and sulfation are absent or depleted and the toxic metabolite N-acetyl-p-benzoquinone-imine (NAPQI) accumulates, causing oxidative injury.
- The principal management for acetaminophen toxicity is the administration of acetylcysteine, although other adjunctive therapies have been described.

79.2 INTRODUCTION

Acetaminophen is an analgesic and antipyretic that is derived from the chemical compound paracetamol (para-amino-phenol). Although acetaminophen is a common and safe over-the-counter analgesic for people, a narrow margin of safety in dogs and cats limits its use in small animal patients. However, these same drug characteristics, and the presence of acetaminophen in most American households, make cases of toxic exposure commonplace for the small animal veterinarian. The American Society for the Prevention of Cruelty to Animals Animal Poison Control Center reported over 1000 cases of accidental acetaminophen exposure from 1998 to 2000.[1] Acetaminophen represents the second most common cause of nonsteroidal antiinflammatory drug (NSAID) toxicity in dogs and cats.[1,2]

79.3 THERAPEUTIC USE OF ACETAMINOPHEN

Acetaminophen is an analgesic which is commonly used in the management of mild to moderate pain when an opioid is not needed and another NSAID is not desired or is contraindicated. The mechanism of analgesia provided by acetaminophen is not well understood but involves an increase of the pain threshold and possible inhibition of cyclooxygenase.[3] Antipyretic effects of the drug are centrally mediated at the level of the hypothalamus.[3] Acetaminophen is a weak prostaglandin inhibitor and therefore has no significant antiinflammatory effects. It is not known to alter platelet function.[3]

79.3.1 Preparations and Routes of Administration

Acetaminophen is available over the counter and by prescription. Oral tablets, liquid preparations, and suppositories are available.[3,4] Acetaminophen is also available in combination with other drugs including opioids, antihistamines, and decongestants. Over 200 prescription and over-the-counter formulations are available, including more than 30 combination preparations.[1,4] Acetaminophen has been used safely in appropriate dosages in dogs. The recommended dosage is 10 to 15 mg/kg PO q 6-12 hr.[1,5] However, concerns about toxicity with inappropriate administration and the availability of alternative analgesics limit the use of acetaminophen in dogs. Acetaminophen is not recommended for therapeutic use in cats because of the unique risk of toxicity in this species.

79.4 PHARMACOLOGY AND PHARMACOKINETICS

Acetaminophen is absorbed rapidly after oral administration.[3-6] Peak blood concentrations typically are reached within 30 to 60 minutes.[5] After absorption, acetaminophen undergoes partial metabolism in the liver by microsomal enzymes. At least 90% of the drug is ultimately metabolized to the nontoxic conjugates (sulfate and glucuronide). A small amount of drug (approximately 5%) is excreted unchanged in the urine. Another 5% of drug is metabolized to a nontherapeutic metabolite (i.e., NAPQI) which becomes important with excessive ingestion.[1,5-8] The half-life of acetaminophen is normally between 0.6 and 3 hours, but may be prolonged in animals with toxic levels of exposure or hepatic disease.[5,6,8] In the dog, glucuronide predominates as the major metabolite excreted in the urine, although sulfate metabolites predominate in the cat.[8] With therapeutic dosing, increased hepatic enzymes may be noted, and with long-term therapy, hepatic injury or failure may occur.[3-5]

79.5 PATHOPHYSIOLOGY OF TOXIC EXPOSURE

Toxicity from acetaminophen occurs when critical metabolic pathways are either absent, deficient, or saturated.[1,6-8] NAPQI is a highly active metabolite that alters the chemical structure of proteins and lipids and causes cellular damage.[1,6] NAPQI can be neutralized by binding with the sulfhydryl groups of endogenous glutathione.[1,6] When glutathione supplies are limited (as in the cat) or depleted (as with toxic exposure in any species), NAPQI accumulates and causes injury. NAPQI is a reactive oxygen species (free radical) that causes injury by binding cellular macromolecules, causing lipid peroxidation of membranes, and inducing direct cell injury and death.[6] In patients with hepatic dysfunction (chronic liver disease) or increased activity of the cytochrome P450 enzyme system (drug-mediated enzyme induction such as with anticonvulsant therapy), toxicity may be more severe or may occur with lower levels of drug exposure.[6] Primary or secondary damage may occur in the liver, red blood cells, kidneys, central nervous system (CNS), and gastrointestinal (GI) tract. Further details and mechanisms of injury are summarized in Table 79-1.

79.6 TOXICITY: DOSAGE AND EXPOSURE

79.6.1 Canine

Toxic exposure in the dog is most commonly reported to be the result of accidental overdose related to dietary indiscretion.[2] Hepatotoxicity is seen at dosages exceeding 75 to 100 mg/kg in the dog. Methemoglobinemia typically occurs in dogs receiving 200 mg/kg.[1,8,9,14]

79.6.2 Feline

Cats may demonstrate clinical signs of toxicity with any level of exposure to acetaminophen. Their increased vulnerability is thought to be related to a reduced glucuronide metabolism and relative deficiency of glutathione compared with other species.[8,9] Cats are more commonly reported to experience acetaminophen overdose from deliberate administration of the drug.[1,2,10] The threshold for methemoglobinemia in cats has been reported as 10 mg/kg.[1] Fatalities may be expected with dosages of 140 mg/kg or greater, although a recent experimental study reported two isolated deaths with a single exposure of 90 mg/kg.[11] Experimental studies and clinical reports suggest that significant individual variation exists in exposed cats, both in the metabolism of acetaminophen and in the vulnerability to oxidative stress.[1,8,10-12]

79.7 CLINICAL SYMPTOMS ASSOCIATED WITH TOXICITY

79.7.1 Four Stages of Toxicity

Four main stages of acetaminophen toxicity have been described.[6,8] Clinical signs of stage I may persist for up to 24 hours and include anorexia, nausea, vomiting, lethargy, and pallor. There are no typical laboratory abnormalities in stage I, and in some cases the animal may be asymptomatic. Stage II occurs 24 to 72 hours after ingestion. Clinical signs include abdominal pain, icterus, any of the signs of stage I, and elevated serum bilirubin and liver enzyme levels. Oliguria may also be noted. Aspartate aminotransferase (AST) level is typically elevated before true hepatic failure or dysfunction occurs and is thought to be the most sensitive enzyme to indicate toxicity. The most severe hepatotoxicity occurs in stage III (72 to 96 hours after exposure). Absence of clinical signs is possible in stage III, but evidence of fulminant liver failure may be present (e.g., marked icterus, prolonged prothrombin time, encephalopathy, or coma) with severe exposures. Stage IV is considered the recovery phase and proceeds over several weeks.

79.7.2 Canine

Toxic exposure typically results in hepatic dysfunction and associated secondary GI and CNS signs in dogs (see Chapter 127, Hepatic Failure). When methemoglobinemia occurs following high levels of drug exposure, altered mucous membrane color (brown or muddy coloration) and respiratory signs secondary to altered oxygen carrying capacity may also be noted. There have been reported cases of dogs experiencing erythrocytic oxidative injury in the absence of significant hepatic injury.[13,14] In addition, a single case report identified a possible association with the acute development of keratoconjunctiva sicca postexposure.[13] Clinical signs of acute renal failure may include oliguria and GI upset such as vomiting, hematemesis, and anorexia (see Chapter 135, Acute Renal Failure).

79.7.3 Feline

Toxic exposure to acetaminophen in the cat typically represents a high-level exposure. As in the dog, clinical signs may include those referable to hepatic or renal failure (see Chapters 127 and 135, Hepatic Failure and Acute Renal Failure, respectively). However, methemoglobinemia and Heinz body formation are more common manifestations of toxicity in cats. This is likely due to the higher level of exposure and increased susceptibility of 335 feline hemoglobin to 336 oxidative injury.[8] Initial signs may be nonspecific and include lethargy, depressed mentation, tachypnea or respiratory distress, signs of GI upset (i.e., anorexia, vomiting, or diarrhea), pale or muddy mucous membranes, and tachycardia. Facial swelling or edema is another common sign in felines and is believed to result from vasculitis. A varied spectrum of neurologic manifestations may occur, ranging from ataxia to coma (see Chapter 103, Hepatic Encephalopathy).[10]

Table 79-1 Mechanisms of Acetaminophen-Induced Injury by Organ System[6,8]

Organ System	Mechanism of Injury	Site of Injury
Hepatic	Binding of NAPQI to sulfhydryl groups within the hepatocytes	Hepatocellular death and central lobular necrosis as NAPQI covalently binds to vital proteins and the lipid bilayer of hepatocyte membranes Location believed to be a result of the higher concentrations of cytochrome P450 around the central vein
Hematologic	Binding of NAPQI and associated oxidative injury to the erythrocyte membrane and hemoglobin molecules	Methemoglobinemia, Heinz body formation, and associated hemolytic anemia Thrombocytopenia has also been reported with toxicities in humans
Renal	Primary renal injury is less common; however, when it does occur the mechanism of injury is likely similar to that associated with direct hepatic injury (cytochrome P450 present in the proximal renal tubules)	Either direct acute renal tubular necrosis, or secondary renal injury via hepatorenal syndrome
Central nervous system	Mechanism of primary injury not well described	Hepatic encephalopathy secondary to hepatic injury Primary neurologic injury may be uncommon Coma reported in some cases of human and feline toxicity
Gastrointestinal	Secondary involvement a consequence of hepatotoxicity Primary gastrointestinal injury uncommon	Gastritis, gastric ulceration, gastric necrosis

*NAPQI,*N-Acetyl-*p*-benzoquinone-imine.

79.8 TREATMENT

In cases of recent acetaminophen exposure (confirmed or suspected), emesis should be induced (see Chapter 77, Approach to Poisoning and Drug Overdose). An animal that has ingested acetaminophen more than 1 hour before presentation may not benefit from emesis, given the rapid absorption of the drug.[6] Appropriately timed administration of activated charcoal can be very beneficial, because acetaminophen is adsorbed rapidly by charcoal. Gastric decontamination with activated charcoal is recommended within 2 hours of drug ingestion. The benefit of administration more than 2 hours after acetaminophen ingestion has not been documented and therefore is not advised in humans, despite the potential influence of enterohepatic circulation.[6,7]

The principal treatment and antidote for acetaminophen toxicity is N-acetylcysteine (NAC).[1,6,7,12] NAC has many mechanisms of action that include both hepatic and systemic effects.[6,7] One important mechanism of NAC as an antidote for acetaminophen toxicity is the provision of additional glutathione for neutralization and direct binding of the toxic metabolite, NAPQI. Details concerning the beneficial mechanisms of NAC therapy are listed in Box 79-1.[6,7] NAC may be administered orally or intravenously (although some formulations are approved for intravenous use, other preparations are commonly used off-label for intravenous administration through a filter).

NAC is available in 10% or 20% solutions. Dilution with isotonic saline, 5% dextrose in water, or sterile water is advised before administration. A loading dose of 140 mg/kg is administered initially intravenously, followed by subsequent doses of 70 mg/kg q6h. Administration is advised for 72 hours following toxic exposure. Adverse effects are not common but may include nausea, vomiting, and anaphylaxis (particularly with intravenous administration of oral preparations).[1,7]

79.8.1 Box 79-1 Mechanisms of Action and Therapeutic Benefit of N-Acetylcysteine

- Increased synthesis and availability of glutathione via conversion of NAC to cysteine
- Direct binding and detoxification of NAPQI via the reduced sulfhydryl group of NAC
- Increased percentage of nontoxic metabolites by supplying substrate for sulfation

NAC, N-Acetylcysteine; *NAPQI,* N-acetyl-*p*-benzoquinone-imine.

Adjunctive therapies for acetaminophen toxicity include vitamin C (ascorbic acid) to facilitate conversion of methemoglobin to reduced hemoglobin (see Chapter 88, Methemoglobinemia), cimetidine for its potential antagonism of the cytochrome P450 pathway, and S-adenosyl-L-methionine because of its potential hepatoprotective and antioxidant effects.[1,9-12,15] Suggested dosages are included in Table 79-2. In addition to specific antidotal therapy, supportive care should be provided as needed (see Chapters 127 and 135 Hepatic Failure and Acute Renal Failure, respectively). Supportive care most often includes intravenous fluid therapy, GI protectants, correction of acid-base abnormalities, and supplemental oxygen when appropriate (see Chapters 19, 64, and 181, Oxygen Therapy, Daily Intravenous Fluid Therapy, and Gastrointestinal Protectants, respectively). Transfusion therapy with whole blood, packed red blood cells, or oxyglobin should be considered when anemia or methemoglobinemia is severe enough to cause signs of decreased oxygen carrying capacity (see Chapter 66, 336 337 Transfusion Medicine). Treatment with methylene blue has been described, but is not advised, especially in the cat in which methylene blue administration may also result in Heinz body formation.[10-12] Hemodialysis is not of benefit.

Table 79-2 Suggested Dosing for N-Acetylcysteine and Adjunctive Therapies[1,9-12,15]

Therapy	Dosing
N-Acetylcysteine[*]	*Canine:* 140 mg/kg IV initial dosage, then 70 mg/kg IV q4-6h for 72 hours *Feline:* Same as canine
Vitamin C (ascorbic acid)	*Canine:* 30 mg/kg PO or IV q6-12h *Feline:* Same as canine
Cimetidine	*Canine:* 5 to 10 mg/kg PO or IV q6-8h *Feline:* Same as canine
SAMe	*Canine:* Initial dosage of 40 mg/kg PO, then 20 mg/kg PO q24h *Feline:* Initial dose of 180 mg PO, then 90 mg q12-24h; or 30-50 mg/kg q24h

IV, Intravenous; *PO,* per os; *SAMe, S*-adenosyl-L-methionine.

[*] May be administered PO or IV. If oral suspension administered IV, use of a filter is advised.

79.9 Monitoring, Recovery Period, and Prognosis

The prognosis depends on the level of toxic exposure, time to initiation of therapy, and the extent of organ damage. Patients with severe hepatotoxicity that fail to recover with aggressive therapy will typically deteriorate within 3 to 5 days. Full recovery from hepatic injury typically occurs over 2 to 3 weeks. Resolution of clinical signs of methemoglobinemia may be expected within 72 hours with proper treatment and supportive care. Successful treatment of cats with toxic exposure is challenging, because the increased susceptibility for high-level exposure and vulnerability to more severe toxicity makes the prognosis for any feline patient guarded unless therapy is initiated within 24 hours.

79.10 Suggested Further Reading[*]

L Aronson, K Drobatz: Acetaminophen toxicity in 17 cats. *J Vet Emerg Crit Care*. **6**, 1996, 65, *The only clinical case series specific to feline toxicoses that includes a review of the unique pathophysiology and considerations for treatment in this species*.

JA Richardson: Management of acetaminophen and ibuprofen toxicoses in dogs and cats. *J Vet Emerg Crit Care*. **10**, 2000, 285, *Authored by a senior veterinarian at the American Society for the Prevention of Cruelty to Animals Animal Poison Control Center; a concise review of the two most common NSAID toxicities seen in dogs and cats*.

NS Taylor, N Dhupa: Acetaminophen toxicity in cats and dogs. *Comp Cont Educ Pract Vet*. **22**, 2000, 160, *A more contemporary veterinary review of toxicosis that provides comprehensive coverage of pathophysiology, clinical signs, and treatment (includes a review of adjunctive therapy)*.

* See the CD-ROM for a complete list of references.

80 Chapter 80 Salicylates

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80.1 KEY POINTS

- Salicylate toxicity represents an infrequent yet serious and complex nonsteroidal antiinflammatory drug toxicity.
- Toxicity may result with acute ingestions of 100 mg/kg in the dog, and 50 mg/kg in the cat.
- Toxicity results when unbound drug in blood and tissue leads to uncoupling of oxidative phosphorylation and disruption of the Krebs cycle, which results in global organ dysfunction.
- There is no antidote for salicylate toxicity.
- The principal treatment for salicylate toxicity involves alkalinization of the urine to increase the rate of drug excretion.
- Hemodialysis is an effective therapy for salicylate toxicity and should be considered in cases with severe neurologic impairment, acute renal failure, refractory acidosis, or patients intolerant of bicarbonate or fluid therapy.

80.2 INTRODUCTION

Salicylates represent perhaps the earliest class of antiinflammatory agents and possess analgesic and antipyretic properties.[1] Aspirin is both the most commonly used and most commonly recognized salicylate. The active ingredient of aspirin is the phenol-derived chemical compound, acetylsalicylic acid.[1] Although replaced in some cases by newer antiinflammatory agents, aspirin remains a common over-the-counter analgesic for humans, with application to small animal veterinary patients as well. Although salicylates represent the third most common cause of nonsteroidal antiinflammatory drug toxicity in dogs and cats, intoxication is seen relatively infrequently by the small animal practitioner.[2] However, salicylate toxicity still represents an important toxicity because of the serious and complex impact on the patient's physiology.

80.3 THERAPEUTIC USE OF SALICYLATES

Salicylates are used commonly to treat mild to moderate pain and fever.[3] The mechanism of analgesia provided by salicylates involves nonselective inhibition of cyclooxygenase (peripherally and centrally mediated).[3,4] Additional antipyretic effects of the drug are centrally mediated at the level of the hypothalamus.[3] Salicylic acid is a potent inhibitor of thromboxane production and, as such, has long been used therapeutically as an antithrombotic agent because of its negative effect on platelet function.[3]

80.3.1 Preparations and Routes of Administration

Salicylates are common ingredients in a variety of prescription and over-the-counter compounds.[5] Aspirin is probably the most familiar source of salicylate for the small animal veterinarian. Other common sources include oil of wintergreen, Pepto-Bismol, Percodan, and BENGAY. As with other antiinflammatory agents, salicylates may be formulated in combination with other drugs (i.e., opioids, acetaminophen, decongestants) and, whether in combination or alone, they are available as oral tablets, liquid suspensions, and topical preparations.[5]

The availability of alternative cyclooxygenase-selective analgesics limits the contemporary use of high-dose aspirin therapy for analgesia in both dogs and cats; however, therapeutic administration of aspirin at appropriate dosage is considered acceptable for both species. The recommended dosage for antiinflammatory or analgesic effect is 10 to 25 mg/kg PO q8-12h for dogs and 10 to 20 mg/kg PO q48-72h for cats.[4,6] Adverse effects with therapeutic use of aspirin include gastrointestinal (GI) upset, mucosal ulceration, acute GI bleeding, and altered hemostasis (primarily irreversible platelet dysfunction that persists for several days).

80.4 PHARMACOLOGY AND PHARMACOKINETICS

Salicylates are absorbed rapidly after oral administration.[3–6] Initial serum levels are detected within 30 minutes of ingestion and peak levels occur within 2 to 4 hours. Sustained release and enteric-coated preparations have less predictable pharmacokinetics. More importantly, massive ingestions cause delayed gastric emptying and, hence, result in serum levels that may continue to rise for several hours.[7,8]

After absorption, aspirin is hydrolyzed in intestinal, hepatic, and red blood cells to form salicylic acid. This active substance reversibly binds to serum proteins (principally albumin). Upon saturation of all available binding sites, any additional ingestion results in a significant increase in free salicylate and a parallel increase in tissue concentrations. Salicylate undergoes renal clearance and may be excreted unchanged or following glucuronidation. A small amount may also undergo conjugation with glycine or hydroxylation before renal excretion. Under circumstances of acute toxicity (rather than therapeutic dosage), metabolic pathways become saturated and clearance is determined by urinary excretion, which in turn is influenced by urine pH.[7–9] It is the urinary excretion rate that determines the drug half-life in these circumstances, and urinary excretion may increase to several times greater than normal. The serum half-life of aspirin in humans following acute intoxication exceeds 30 hours.[7,9] In cats the serum half-life is normally quite long (35 to 40 hours), thus creating less of a prolongation of half-life following toxic exposure. The normal half-life in the dog (with therapeutic administration) is between 6 and 9 hours.[4] However, the relative effect of toxic ingestion on serum half-life in the dog would be expected to parallel the effect seen in humans.

80.5 TOXICITY: DOSAGE AND EXPOSURE

80.5.1 Canine

Salicylate toxicosis in the dog most commonly results from accidental ingestion.[2] However, deliberate but inappropriate administration by an owner or veterinary professional can also result in toxicosis. The level of exposure capable of causing toxicosis is not clear, perhaps due in part to variable susceptibility among individuals.[11] GI signs alone may occur with dosages of 50 mg/kg.[4,11] Severe signs of toxicity are reported to occur over a wide dosage range of 100 to 500 mg/kg.[11]

80.5.2 Feline

Cats are more susceptible to salicylate toxicity, because this species is deficient in glucuronidation pathways. Cases of toxicosis in this species are most often the result of inappropriate administration. Cats may experience toxicosis at dosages exceeding 50 mg/kg, but severe toxicosis was not seen in an experimental setting until repeated exposures greater than 80 mg/kg were administered.[11] Similarly, the threshold for lethal exposure is not clear, but any exposure exceeding 100 mg/kg should be considered serious, with the potential for lethality.

80.6 PATHOPHYSIOLOGY OF TOXIC EXPOSURE

Toxicity from salicylates results from uncoupling of oxidative phosphorylation and disruption of the Krebs cycle.[7–9] This mechanism of toxic injury affects multiple organ systems in high-level exposures. Minor exposure may result predominantly in GI signs (i.e., vomiting, nausea, or diarrhea), and toxicity in such cases is predominantly mediated by the direct antagonism of prostaglandins in the GI tract, which normally serve to increase epithelial cell turnover and mucus and bicarbonate secretion.[2,4] Severe toxicities result in respiratory alkalosis (via direct central stimulation) or a mixed acid-base abnormality (typically characterized by a metabolic acidosis and respiratory alkalosis).

Initial effects of a toxic ingestion include direct stimulation of the respiratory center resulting in tachypnea and a primary respiratory alkalosis. The respiratory alkalosis results in a compensatory loss of bicarbonate via urinary excretion. Ultimately, the compensatory excretion of bicarbonate will exacerbate the impending metabolic acidosis. Uncoupling of oxidative phosphorylation leads to an accumulation of organic acids, predominantly lactic acid and ketoacids. It is these organic acids which contribute the most to the resultant metabolic acidosis and increased anion gap. The specific contribution of the salicylic acid itself exerts a minimal contribution to the anion gap.[7–9] A list of organ systems affected by toxic exposure, the associated mechanisms of injury, and their clinical signs are summarized in Table 80-1. Susceptible organ systems include the central nervous system (CNS), the respiratory system with potential development of noncardiogenic pulmonary edema, and kidneys (acute renal failure [ARF]).

80.7 CLINICAL SIGNS ASSOCIATED WITH TOXICITY

Minor exposure may result predominantly in GI signs (vomiting, nausea, or diarrhea). Major toxicities result in respiratory alkalosis, or a mixed acid-base abnormality (typically characterized by a metabolic acidosis and respiratory alkalosis), and are often accompanied by organ dysfunction or failure.[2,4,7,9] Neurologic involvement may range from altered mental status to coma. In addition, seizure activity (independent of other metabolic causes) has been reported in the dog.[10] Signs of noncardiogenic pulmonary edema include crackles on auscultation, increased respiratory rate and effort, and dyspnea. Altered renal function as a direct effect of toxicity and as a secondary effect of other organ dysfunction may result in electrolyte, acid-base, and fluid imbalances.[7,9] Common electrolyte abnormalities include hypokalemia and hyponatremia. The dominant acid-base status depends on the balance of both respiratory (hyperventilation and compensatory loss of bicarbonate) and metabolic effects (accumulation of organic acids with the concurrent loss of bicarbonate) of toxicity. ARF (especially if associated with oliguria) increases the risk of fluid overload and has the potential to exacerbate a concurrent noncardiogenic pulmonary edema. Thus clinical signs may include vomiting, hematemesis, diarrhea, melena, lethargy, anorexia, dehydration, tachypnea or dyspnea, abnormal respiratory auscultation findings (increased lung sounds or crackles), weakness, depression, coma, and seizure activity. Neurologic signs may be more frequent in cases of chronic salicylism (when repeated doses in excess of therapeutic dosages are administered).[10,11] Common clinicopathologic findings might include altered acid-base status, electrolyte derangements (typically hypokalemia or hyponatremia), azotemia, and hypoglycemia.

80.8 TREATMENT

If the patient presents for treatment within an hour of known or suspected ingestion of aspirin or another source of salicylate, emesis should be induced (see Chapter 77, Approach to Poisoning and Drug Overdose). Following induced emesis, or if emesis is no longer warranted, activated charcoal (with sorbitol) should be administered. In human medicine the use of multidose activated charcoal (MDAC) has been considered but remains controversial.[7–9] The specific indications for MDAC include massive toxicities (large quantities of aspirin have been known to form concretions and be retained within the stomach for extended periods), ingestion of sustained release preparations, and ingestion of enteric-coated preparations.[8] The use of MDAC has also been referred to as *GI dialysis*. Repeated doses of activated charcoal may be administered every 3 to 4 hours until a measurable decrease in blood salicylate levels is noted.[7,8]

There is no antidote or principal treatment for salicylate toxicity; thus the primary objective following decontamination is to optimize excretion of the drug and its metabolites.[7–9] The most effective therapy for this 339 purpose is 340 urine alkalinization. Alkalinization of the urine prevents back-diffusion of metabolites, significantly increases clearance, and thus decreases the half-life of salicylates. Goal-directed administration of sodium bicarbonate may be instituted and continued to maintain a urine pH between 7.5 and 8 and a blood pH between 7.35 and 7.5. Successful alkalinization of the urine has been shown to increase renal excretion by 10-fold to 20-fold, but should not be performed without regard for effects on systemic acid-base status.[7–9] Additionally, prevention of hypokalemia is important, because potassium reabsorption prevents excretion of an alkaline urine because of exchange of potassium for hydrogen in the distal tubule. Hypokalemia is a common sequela of salicylate toxicity, and prophylactic supplementation with potassium chloride as an intravenous fluid additive may be considered early in therapy.

Table 80-1 Clinical Signs and Mechanisms of Salicylate-Induced Injury by Organ System[7–9]

Organ System	Mechanism of Injury	Site of Injury or Clinical Signs
Central nervous system	Direct stimulation	Stimulation of respiratory center leads to primary respiratory alkalosis
	Uncoupling of oxidative phosphorylation	Decreased glucose in CSF and brain (independent of plasma glucose)
Respiratory or pulmonary	Increased pulmonary capillary permeability (possibly via inhibition of prostacyclin or altered platelet-vessel interactions)	Noncardiogenic pulmonary edema
Renal	Compensatory response to respiratory alkalosis	Increased renal excretion of sodium, potassium, bicarbonate
	Direct increase in tubular permeability	Additional loss of potassium, imbalance of sodium and water
	Uncoupling of oxidative phosphorylation	Additional potassium loss due to inhibition of active transport
	Decreased renal blood flow with or without direct renal injury	Acute renal failure (may be nonoliguric or oliguric)
	Salicylate-induced inappropriate antidiuretic hormone	Oliguria
Hepatic and metabolic	Disruption of Krebs cycle and inhibition of dehydrogenases	Increased production of lactate and pyruvate (important source of metabolic acidosis)
	Increased lipolysis	Increased production and accumulation of ketone bodies
	Uncoupling of oxidative phosphorylation	Increased systemic metabolism and tissue glycolysis (typical sequelae include: increased body temperature; increased CO_2 production; increased O_2 consumption; hypoglycemia)
Gastrointestinal	Direct injury with or without prostaglandin-mediated injury	Gastric irritation or ulceration, GI hemorrhage, vomiting
	Direct central stimulation of the chemoreceptor trigger zone	Vomiting (contributes to dehydration, loss of potassium)
Coagulation	Antagonism of vitamin K (direct effect of salicylate analogous to that of warfarin)	Drug-related coagulopathy with prolongation of prothrombin time
	Irreversible inhibition of platelet function	Decreased platelet aggregation, altered primary hemostasis

CO_2, Carbon dioxide; *CSF,* cerebrospinal fluid; *GI,* gastrointestinal; *O_2*, oxygen.

Intravenous fluid therapy should be instituted for maintenance hydration or to replace fluid deficits in patients with GI signs or evidence of dehydration. However, aggressive fluid therapy is of no specific benefit to drug excretion beyond urine alkalinization. Therefore diuresis should be avoided because of the risk of fluid overload in the patient with severe toxicity. Inappropriate fluid administration in cases of severe toxicity may lead to pulmonary and cerebral edema.

A urinary catheter may be beneficial for several reasons in patients with moderate to severe toxicity. Urine pH can be monitored, providing the most efficient means of targeting bicarbonate therapy to alkalinize the urine to effectively increase drug excretion. An indwelling urinary catheter also allows for quantitative monitoring of urine production to guide fluid therapy, particularly in those patients who are at risk for ARF.

Adjunctive therapies that have been suggested for significant toxic exposure include dextrose supplementation and mannitol. Dextrose may be added to intravenous fluid based on serial monitoring of blood glucose levels or may be administered empirically. Because salicylate toxicity may be associated with neuroglycopenia despite normal blood glucose levels, empiric intravenous supplementation with 2.5% to 5% dextrose may be of benefit.[7,8,12] Mannitol administration should be considered on an individual basis when clinical signs of cerebral edema or oliguric renal failure are noted. Caution should be exercised in patients with pulmonary edema.

A checklist of therapeutic considerations for cases of moderate to severe toxicity (either confirmed high-level exposure over 100 mg/kg or with clinical signs of CNS, acid-base, or renal involvement) is provided in Box 80-1. Additional supportive care should include GI protectants (see Chapter 181, Gastrointestinal Protectants) and transfusion therapy (see Chapter 66, Transfusion Medicine) when indicated.

Hemodialysis may be of benefit in cases of acute or severe salicylate toxicity. The decision to pursue hemodialysis 340
in an individual patient is unlikely to be made based on a single criterion; however, refractory acidosis, severe 341
neurologic impairment, overhydration, and ARF are findings that warrant a discussion about dialysis.[7,8,12] Patients with ARF may benefit from peritoneal dialysis when hemodialysis is not available.

80.8.1 Box 80-1 Therapeutic Checklist for the Patient With Salicylate (Aspirin) Toxicity

- Intravenous catheterization and initial blood sample collection
- Gastric decontamination
- Urinary catheterization
    - Consider with moderate to severe intoxications (acute ingestion over 100 mg/kg, or cases with clinical signs of organ dysfunction)
    - Facilitates efficient monitoring of urine pH and urine production
- Intravenous fluid administration
    - Shock fluid therapy if needed (up to 90 ml/kg [dog] or 60 ml/kg [cat]) of intravenous isotonic fluid
    - Estimate dehydration and ongoing losses; replace over 12 to 24 hours in addition to maintenance fluid therapy

  - Consider prophylactic supplementation with potassium chloride (10 to 20 mEq/L)
  - Consider empiric administration of dextrose (2.5% to 5%) as a fluid supplement (for potential neuroglycopenia)
- Urine alkalinization with sodium bicarbonate (to increase drug clearance)*
  - Initial administration of 1 to 2 mEq/kg diluted 1:1 with sterile water and administered as a slow bolus
  - Continued infusion of sodium bicarbonate diluted in sterile water to achieve and maintain urine pH between 7.5 and 8.0 with concurrent blood pH between 7.35 and 7.50
  - Monitor urine pH and blood pH every 2 to 4 hours after achieving target urine alkalinization
- Monitoring
  - Serum potassium concentration
    - Supplement with potassium chloride as needed to prevent and manage hypokalemia
    - Hypokalemia will prevent effective urine alkalinization and impede drug clearance
  - Serum glucose concentration
  - Acid-base status (preventing systemic acidosis)
  - Urine output and volume status
    - Consider mannitol for early signs of oliguric renal failure
    - Consider hemodialysis for severe oliguria, intolerance of bicarbonate therapy, severe neurologic impairment, pulmonary edema, or refractory acid-base and electrolyte abnormalities
- Blood oxygenation and development of pulmonary edema
- Neurologic status
  - Consider mannitol (0.5 to 1.5 g/kg) for signs of cerebral edema

NOTE: Contraindicated if hypercapnia is present.

80.9 MONITORING, RECOVERY PERIOD, AND PROGNOSIS

The patient with moderate to severe salicylate toxicity warrants frequent monitoring of electrolytes, acid-base status, blood glucose concentration, and urine output. In patients with neurologic impairment, serial neurologic examinations should be performed. Close monitoring of respiratory status, blood oxygen saturation, and judicious fluid therapy are appropriate in any patient with acute toxicity. Careful monitoring allows the clinician to assess for the development or progression of pulmonary edema and provide oxygen supplementation when needed.

In humans, one of the most significant contributions to prognosis is the early recognition of toxicosis and rapid institution of therapy.[8] Although salicylate toxicity can be fatal and significant morbidity can be seen with high-level ingestions, with early, aggressive treatment and close monitoring, recovery is possible in most cases.

80.10 SUGGESTED FURTHER READING*

SL Curry, SM Cogar, JL Cook: Nonsteroidal anti-inflammatory drugs: a review. *J Am Anim Hosp Assoc*. **41**, 2005, 298, *A recent review of the pharmacology of NSAIDS in current veterinary use that includes a review of aspirin therapy, adverse effects of therapy, and a brief mention of toxicity*.

DB Jack: One hundred years of aspirin. *Lancet*. **350**, 1997, 437, *A historical review of salicylates and the development and use of aspirin*.

D Villar, WB Buck, JM Gonzalez: Ibuprofen, aspirin, and acetaminophen toxicosis and treatment in dogs and cats. *Vet Hum Toxicol*. **40**, 1998, 156, *A review by ASPCA veterinarians of NSAID toxicosis that includes a discussion of the variable sensitivity to aspirin across species and from individual to individual*.

* See the CD-ROM for a complete list of references

81 Chapter 81 Illicit Drugs

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81.1 KEY POINTS

- Illicit drug intoxication is not uncommon in dogs but is rarely seen in cats.
- Owners rarely volunteer information regarding potential illicit drug exposure but are usually more forthcoming during direct questioning.
- Most intoxications result from ingestion of the drug.
- Unlike other intoxications, animals are usually presented to the veterinarian once clinical signs have become apparent. Urine testing is available for many illicit drugs.
- Amphetamines are indirect-acting sympathomimetic amines, and clinical signs result from enhanced adrenergic stimulation and serotonin syndrome. The hyperdynamic state can result in severe hyperthermia with rhabdomyolysis, neurologic dysfunction, acute renal failure, and metabolic abnormalities.
- Cannabis intoxication results in neurologic and gastrointestinal signs and usually carries a good prognosis.
- Cocaine inhibits presynaptic neuronal uptake of dopamine, norepinephrine, and serotonin, and causes blockade of fast sodium channels. This commonly results in neurologic abnormalities and cardiac arrhythmias.
- Opioid ingestion often leads to sedation, respiratory depression, and bradycardia. Effects can be reversed with naloxone.
- Phencyclidine is a dissociative anesthetic that antagonizes N-methyl-D-aspartate operated calcium channels. Marked central nervous system depression or stimulation may occur.
- Treatment of animals with illicit drug intoxications typically involves emesis, gastrointestinal decontamination, and supportive care. Additional therapies are recommended for specific drug ingestions.

81.2 INTRODUCTION

Animals ingesting illicit drugs rarely are presented to the emergency veterinarian before clinical signs have become apparent. Clinical signs will depend on the class of drug, amount ingested, and time from ingestion, but animals typically have sudden-onset altered neurologic activity including abnormal behavior, ataxia, and anxiety. Some animals may vomit secondary to intestinal foreign body obstruction after ingesting whole bags of drugs.

Owners will rarely volunteer a history of illicit drug ingestion although they will occasionally report stories such as the dog “may have gotten into something at the park.” Direct questioning, asking if family members may have illicit drugs, and allowing time for families to discuss this may be helpful. An explanation that illicit drug intoxication, if treated rapidly and correctly, usually carries a good prognosis and will negate the need for an extensive neurologic workup, will typically encourage people to be more forthcoming with information. A urine drug screen using a point-of-care test strip (Medimpex United, Bensalem, PA) or submission to a toxicology laboratory will confirm suspicion.

If a patient presents within 4 hours of illicit drug ingestion, steps should be taken to decrease absorption and hasten elimination of the drug (see Chapter 77, Approach to Poisoning and Drug Overdose). If there is no contraindication to emesis (seizures, depression), then vomiting should be induced immediately with apomorphine or hydrogen peroxide (dogs). Cats are preferably given xylazine for emesis induction. Activated charcoal should then be administered to adsorb any remaining drug. Sodium sulfate (250 mg/kg in dogs and cats) or a 70% sorbitol solution (1 to 2 ml/kg) may be administered as a cathartic. However, within an hour of ingestion, animals are likely to have clinical signs that contraindicate emesis induction. General anesthesia, intubation, and gastric lavage should be considered in these cases.

Dogs that work for police and customs are at an increased risk of illicit drug intoxication. Veterinarians can educate handlers to recognize the clinical signs, induce emesis, and provide supportive care until veterinary assistance can be reached.

Emergency veterinarians should be familiar with the mechanisms of action, clinical signs, antidotes, if available, and necessary supportive care indicated for animals ingesting the commonly abused recreational drugs. Animal intoxications often mirror trends of illicit drug use in humans.

81.3 AMPHETAMINES

81.3.1 Pharmacology

Amphetamine (α-methyl-phenethylamine or “speed”) and its active dextro isomer dextroamphetamine, methamphetamine (“ice”), methylenedioxymethamphetamine (MDMA or “ecstasy”), and other derivatives are stimulants used by people with attention deficit disorder, to suppress appetite, to reduce fatigue, and to enhance mood. They are examples of indirect-acting sympathomimetic amines with potent central nervous system (CNS) and cardiovascular stimulatory effects.

Amphetamines are structurally similar to norepinephrine but have only a weak action on adrenergic receptors. They enhance monoamine release from nerve terminals in the brain. Norepinephrine and dopamine are the most important monoamine mediators, with clinical signs that result from postsynaptic adrenergic receptor agonism by these catecholamines. Serotonin is also released from the nerve terminal, which may lead to serotonin syndrome (see Chapter 91, Serotonin Syndrome).

81.3.2 Case Management

Decontamination strategies should be implemented if an animal presents within 30 minutes of amphetamine ingestion (see previous section). Emesis and gastric lavage have little effect after this time, because amphetamines are absorbed rapidly from the gastrointestinal (GI) tract, and clinical signs develop after 30 minutes and last 4 to 6 hours. Activated charcoal should be considered and, with the availability of sustained release amphetamine formulations, repeated doses may be warranted.

Initial clinical signs are similar to those seen with other illicit drugs (i.e., cocaine and methylxanthines) and the effects are dose dependent. These include restlessness, excitability, mydriasis, vomiting, tachycardia, tachypnea, hypertension, and hyperthermia. The owner of an animal manifesting restlessness, excitability, mydriasis, and tachycardia should be questioned carefully as to the possibility of amphetamine exposure. A urine illicit drug screen will confirm suspicion (Color Plate 81-1). Treatment of patients with mild clinical signs is supportive and includes intravenous fluid administration, benzodiazepine therapy to control anxiety and excitability, and careful monitoring of heart rate and rhythm, temperature, and neurologic signs.

With high-dose intoxications, cardiovascular and neurologic effects will result in severe hyperthermia. Clinical signs and their progression are then related to the degree of hyperthermia. The patient will be tachycardic and may exhibit cardiac arrhythmias, seizures, and coma. Consequences of amphetamine-induced hyperthermia have been reported in both dogs and humans and include rhabdomyolysis, disseminated intravascular coagulopathy, acute renal failure, hepatic necrosis, and GI ulceration.[1] Treatment should be directed toward aggressive cooling, maintenance of normal cardiovascular function, adequate sedation and cessation of seizure activity with benzodiazepines, IV fluids for potential rhabdomyolysis and renal failure, and prevention of progression to multiorgan failure (see Chapters 167 and 186, Heat Stroke and Anticonvulsants, respectively). Treatment of hypertension with α-blockers, calcium channel antagonists, or nitroprusside may be necessary (see Chapter 178, Antihypertensives). Chlorpromazine and haloperidol may antagonize the effects of amphetamines (and cocaine) by antagonizing or blocking catecholamines.

Urinary acidification to increase the renal elimination of amphetamines has been recommended by some authors. However, this may increase myoglobin precipitation within the tubules and lead to renal failure.

There are reports in the human literature of fatal “water intoxication” in humans that is secondary to MDMA (3,4 methylene-dioxymeth-amphetamine or ecstasy) intoxication.[2] A syndrome of inappropriate antidiuretic hormone (SIADH) secretion in combination with excessive water consumption leads to free-water retention, acute hyponatremia, and cerebral edema (see Chapter 54, Sodium Disorders).

81.3.3 Outcome and Prognosis

Animals presented after recently ingesting amphetamines and showing no clinical signs have an excellent prognosis following GI decontamination. Those having mild clinical signs of tachycardia, anxiety, and mild hyperthermia have a good prognosis with supportive care and monitoring. There is little information in the literature regarding prognosis in dogs with severe clinical signs, but one case report documents the development of multiorgan failure and death in a 1-year-old dog 9 hours after ingestion of fenproporex (N-alkylated amphetamine derivative).[3] Rapid recognition and appropriate treatment of patients with hyponatremia and aggressive treatment of hyperthermia will lead to a better chance of survival.

81.4 CANNABIS

81.4.1 Pharmacology

Extracts from *Cannabis sativa* contain numerous cannabinoids, the most pharmacologically active and abundant of which is 9-tetrahydrocannabinol (THC). The dried leaves and flowers of the hemp plant are known as *marijuana* or *grass,* and the extracted resin is called *hashish*. However, as with other recreational drugs, there are countless street names.

Cannabinoids bind to specific central and peripheral G-protein–linked cannabinoid receptors and interact with the central neurotransmitters norepinephrine, dopamine, serotonin, and acetylcholine. Marijuana is absorbed rapidly and eliminated slowly. In a retrospective study of 213 cases of marijuana toxicosis in dogs, all animals made full recoveries with the greatest ingested dose of marijuana reported as 26.8 g/kg.[4] Clinical signs were seen with doses as low as 85 mg/kg, but fatalities are rare because of the large therapeutic index of THC. Neurologic signs occurred in nearly all of these cases, and GI signs were documented in approximately 30 cases. Intoxication in dogs usually results from ingestion of marijuana cigarettes, loose marijuana, and cookies or brownies containing the drug.

81.4.2 Case Management

Animals are uncommonly presented for known cannabis ingestion unless clinical signs are apparent. Presenting complaints may include behavior changes, depression, ataxia, tremors, and weakness. Vomiting is common, although cannabinoids do have antiemetic effects. Vasodilation is marked in the scleral and conjunctival vessels and gives a “blood-shot” appearance. Affected animals may be tachycardic or bradycardic. Severe intoxications may result in coma or seizures. A urine drug screen will confirm cannabis exposure.

GI decontamination emesis induction and repeated doses of activated charcoal with a cathartic should be given because of extensive enterohepatic circulation (if there are no contraindications).

Close monitoring with supportive care and minimal stimulation is usually all that is required for these patients. However, with more severe intoxications neurologic, hemodynamic, ventilatory, and thermoregulatory support may be needed.

81.4.3 Outcome and Prognosis

The prognosis for cannabis-intoxicated animals is generally excellent. However, severe intoxication with marked neurologic signs will carry a worse prognosis.

81.5 COCAINE

81.5.1 Pharmacology

Cocaine is an alkaloid derived from the leaves of the South American shrub *Erythroxyline coca*. It is available in the pure free base (“crack,” ≥90% cocaine) and the less pure water-soluble hydrochloride salt (12% to 60%). It is rapidly absorbed across all mucosal surfaces and has a short half-life (duration of action of 30 minutes when given intravenously). Originally used by natives of South America to reduce fatigue while working at high altitudes, it has been abused for over a century in Western countries for its psychomotor stimulant effects. When given intravenously to experimental dogs, convulsions began at a mean dosage of 11.8 mg/kg.[5] The mean lethal dose in the same study was 21 mg/kg. 343 344

Cocaine inhibits presynaptic neuronal reuptake of norepinephrine, dopamine, and serotonin, thus increasing synaptic and circulating levels of these hormones. It also blocks fast sodium channels (like other type I antiarrhythmic agents), slowing conduction during phase 0 of the action potential, thereby blocking cell conduction. Cocaine therefore has local anesthetic activity; enhances sympathetic transmission causing tachycardia, cardiac arrhythmias, and increased arterial pressure; and has central effects of excitement and euphoria.

81.5.2 Case Management

Animals will usually be presented to a veterinarian with clinical signs of restlessness, excitement, and hyperesthesia that may progress to seizures in cases with severe intoxications. The patient may vomit as a result of stimulation of the area postrema in the medulla (chemoreceptor trigger zone). Initial respiratory stimulation may progress to respiratory depression. Although bradycardia is reported as an early clinical sign, most animals will typically be tachycardic and hypertensive because of the sympathomimetic effects of cocaine. This hyperdynamic state may result in hyperthermia, hypoglycemia, and a lactic acidosis. Confirmation can me made with a urine illicit drug screen (see Color Plate 81-1).

Decontamination strategies will have a small role because of the rapid absorption of cocaine. Goals of therapy include maintenance of normal ventilation, reduction of CNS activity, treatment of cardiac arrhythmias, resolution of hyperthermia (see Chapter 167, Heat Stroke), and correction of metabolic and acid-base derangements. Control of seizures and anxiety can usually be achieved with benzodiazepines. An electrocardiogram is important to identify arrhythmias. Cardiac effects of cocaine are dose dependent and include sinus bradycardia and ventricular premature contractions at lower doses, and supraventricular or ventricular tachycardia at higher plasma levels.[6] Benzodiazepines are effective for reducing sympathetic outflow from the CNS and therefore reducing sympathetic-induced arrhythmias. However, they have no effect on the myocardial sodium channel blockade that predominates in the pathophysiology of cocaine-induced ventricular arrhythmias. Advanced Cardiac Life Support (ACLS) guidelines published in 2001 recommend sodium bicarbonate or lidocaine as the first-line therapy for cocaine-related ventricular tachycardia/ventricular fibrillation, whereas propranolol was contraindicated.[7] Sodium bicarbonate improves electrocardiographic changes and myocardial function secondary to experimental cocaine toxicity in dogs.[8] It is not known if the effects of sodium bicarbonate are due to a change in sodium load or secondary to an increase in pH. There is still much controversy as to the use of lidocaine in the treatment of cocaine-induced arrhythmias because of fear of lowering the seizure threshold and potentiating cocaine toxicity.

Chlorpromazine and haloperidol may antagonize the effects of cocaine by antagonizing or blocking catecholamines.

81.5.3 Outcome and Prognosis

Animals presented with mild clinical signs have a good prognosis with supportive care and intensive monitoring. Patients with severe cardiac and neurologic abnormalities, or those that are hyperthermic, have a more guarded prognosis.

81.6 OPIOIDS

81.6.1 Pharmacology

The term *opioid* refers to any synthetic or naturally occurring substance that produces morphine-like effects and is blocked by the opioid antagonist naloxone. The term *opiate,* although commonly used interchangeably with *opioid,* applies only to synthetic morphine-like drugs with a nonpeptide structure.[9]

Opium is an extract of the juice of the poppy plant *Papaver somniferum* and has been used for thousands of years to induce euphoria, sleep, and analgesia and to stop diarrhea. Small animals may suffer from opioid intoxication secondary to veterinary administration (e.g., morphine, methadone, hydromorphone, fentanyl), ingestion of prescribed opioids (e.g., fentanyl patches, codeine), or ingestion of recreational opioids (e.g., diacetylmorphine [heroin]). Opioids have effects at G-protein–linked opioid receptors (μ, δ, and κ) predominantly found in the CNS and GI tract. Neuronal excitability is reduced secondary to increased membrane potassium conductance and inhibition of calcium entry, with central cholinergic, serotoninergic, adrenergic, and dopaminergic systems all being affected. Opioids are used clinically for their analgesic properties, but commonly seen side effects of euphoria/dysphoria, respiratory depression, nausea/emesis, bradycardia, pupillary constriction, and decreased GI motility are seen with routine clinical use and secondary to intoxication.

81.6.2 Case Management

Animals may be presented to the veterinarian with a known history of opioid ingestion (e.g., fentanyl patch belonging to a person or animal) or iatrogenic opioid overdose. Some owners may not be aware of intoxication or may not volunteer this information. Animals may look nauseous or be vomiting, having diarrhea, panting, or hypoventilating (evidenced by increased partial pressure of arterial carbon dioxide), and/or be ataxic, depressed, or even comatose. Pupils will be constricted initially (dogs only; cats develop mydriasis), but if respiratory depression and neurologic signs are severe, they may become dilated secondary to hypoxia. Despite central respiratory depression, cardiovascular function is relatively spared. A tentative diagnosis can be made with a urine illicit drug screen or following to a positive response to a naloxone response test.

Treatment is based on GI decontamination, reversal of the opioid-induced effects with the antagonist, naloxone, and supportive care. Apomorphine can be administered if there are no contraindications to emesis induction. Although a chemically related compound, apomorphine does not bind to opioid receptors and exerts its emetic effects through dopamine agonism. Repeated doses of activated charcoal should also be given.

Signs of opioid intoxication can be reversed with the antagonist naloxone. An initial dose of 0.01 mg/kg IV 344
should be given and the response noted. Several doses may be necessary before signs improve. Depending on the 345
half-life of the opioid, repeated doses or a constant rate infusion may be required to prevent renarcotization.

Supportive care is important until the patient has normal neurologic, ventilatory, hemodynamic, and thermoregulatory function. If the patient is hypoxemic, supplemental oxygen should be provided. If a gag reflex is absent or the patient is hypercapnic despite opioid reversal with naloxone, endotracheal intubation and mechanical ventilation are indicated.

81.6.3 Outcome and Prognosis

Rapid recognition of opioid intoxication with appropriate supportive care and reversal with naloxone will improve the prognosis. If intervention for a patient is delayed, and the patient is severely hypoxemic or has been subjected to prolonged hypoxemia, the prognosis is more guarded. A positive response to therapy is the best prognostic indicator in these cases.

81.7 PHENCYCLIDINE

81.7.1 Pharmacology

Phencyclidine (PCP) (5% to 90% pure) and ketamine are dissociative anesthetic agents that are used commonly as recreational drugs. PCP was developed as a human intravenous anesthetic but was found to have too many psychomimetic effects following recovery and is now no longer used for this purpose. Ketamine is a closely related agent that is not used commonly as an anesthetic agent in humans, but is used frequently in veterinary patients and human pediatric patients.

Dissociative anesthetics noncompetitively antagonize N-methyl-D-aspartate–operated calcium channels. They also act on the δ-receptor that is believed to mediate the effects of dysphoria and the hallucinations produced by certain opioids. PCP is rapidly absorbed. Clinical signs from the experimental intoxication of a conscious dog with 1 mg/kg IV of PCP included increased motor activity, jaw snapping, tremors, rigidity, nystagmus, seizures, and opisthotonus before death.[10] Cardiovascular signs such as tachycardia and hypertension may be seen along with hyperthermia. In severe cases, respiratory depression can occur.

81.7.2 Case Management

Patients may be presented following recent ingestion of PCP or may already have clinical signs related to the exposure. If clinical signs are minimal and there are no contraindications, emesis should be induced. This should be followed by administration of repeated doses of activated charcoal and a cathartic, because there is extensive enterohepatic recirculation of PCP. Induction of anesthesia followed by intubation and gastric lavage should be considered in severely affected animals.

Animals with mild signs should be kept quiet in a cool, dark area with minimal stimulation and anxiety controlled with benzodiazepines. Respiratory, hemodynamic, neurologic, and thermoregulatory care are essential in these patients and in animals with more severe clinical signs.

Treatment of animals with severe neurologic signs is based on controlling seizures with benzodiazepines and attempting to maintain cerebral perfusion pressure and oxygen delivery (see Chapter 100, Intracranial Hypertension). Strategies include the administration of mannitol to reduce cerebral edema, elevation of the patient's head at a 15-degree to 30-degree incline, prevention of jugular compression, and maintenance of normocapnia. Mechanical ventilation may be necessary if an animal is hypoventilating. Strategies to ensure normoglycemia and prevent hyperthermia should also be employed.

81.7.3 Outcome and Prognosis

With appropriate supportive care, animals presented with mild clinical signs generally return to a normal state within hours of arrival. Dogs with severe neurologic, cardiovascular, or respiratory dysfunction have a more guarded prognosis, but aggressive and appropriate supportive care will increase patient survival.

81.8 SUGGESTED FURTHER READING*

JD Catravas, IW Waters: Acute cocaine intoxication in the conscious dog: Studies on the mechanism of lethality. *J Pharmacol Exp Ther*. **217**, 1981, 350, *Experimental study of cocaine administration to conscious dogs. Coadministration of diazepam, propanolol, and pimozide, as well as the effect of a decreased ambient temperature, evaluated also*.

P Janczyk, CW Donaldson, S Gwaltney: Two hundred and thirteen cases of marijuana toxicoses in dogs. *Vet Hum Toxicol*. **46**, 2004, 19, *Large retrospective case series of marijuana in dogs*.

HP Rang, MM Dale, JM Ritter, PK Moore: Analgesic drugs. In HP Rang, MM Dale, JM Ritter, PK Moore (Eds.): *Pharmacology*. ed 5, 2003, Churchill Livingstone, Edinburgh, *An excellent review of opioid pharmacology*.

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* See the CD-ROM for a complete list of references

82 Chapter 82 Rodenticides

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82.1 KEY POINTS

- Rodenticide intoxication is common in the dog and seen occasionally in the cat.
- The clinician must identify which rodenticide has been consumed.
- Unless contraindicated, decontamination techniques should be performed immediately following acute ingestion.
- Anticoagulant rodenticide exposure will most commonly cause body cavity or pulmonary parenchymal bleeding.
- Treatment of patients with rodenticide-induced coagulopathy consists of fresh frozen plasma to correct the coagulopathy, vitamin K to enable production of active coagulation factors, and supportive care.
- Coagulopathy due to anticoagulant rodenticide exposure has an excellent prognosis if treated appropriately.
- Bromethalin intoxication leads to cerebral edema and severe neurologic signs, and is associated with a poor prognosis.
- Cholecalciferol intoxication results in hypercalcemia. This can lead to soft tissue mineralization, acute renal failure, and cardiac arrhythmias.
- Zinc phosphide and strychnine are restricted-use pesticides. Intoxication is therefore uncommon, although secondary intoxication from the ingestion of poisoned rodents is possible.

82.2 INTRODUCTION

Rodenticide ingestion is a common intoxication in dogs. Anticoagulant rodenticide intoxications are most frequently presented to the emergency veterinarian, but bromethalin and cholecalciferol are also seen. It is essential that the correct rodenticide be identified; treatment for the wrong intoxication could lead to the death of the animal. Owners should be encouraged to bring in rodenticide packaging for identification of the active ingredient. Animal Poison Control Center can give excellent advice to aid in identification of the rodenticide as well as treatment of these patients.

In most cases the ingestion has been witnessed and the dog or cat is taken immediately to the emergency clinic before the onset of clinical signs. Other animals will present with signs of intoxication. Presenting complaints and clinical signs will vary with the type of rodenticide ingested. Careful questioning of the owner should be performed during the history. Asking, “Is there any rat poison on your property?” rather than “Is there any chance that your dog has gotten into rat poison?” will often result in a more useful response.

The goal of treatment depends on how soon after ingestion the animal is presented. Decontamination of the animal to prevent rodenticide absorption is key following acute ingestion, whereas alternative treatment and supportive care are needed for patients that have clinical evidence of intoxication.

The mechanism of action, pathologic consequences, and published lethal dose[1] of common rodenticides are shown in Table 82-1.

82.3 ANTICOAGULANT RODENTICIDES

82.3.1 Pathophysiology and Clinical Signs

Animals that consume a sufficient amount of an anticoagulant rodenticide develop clinical signs secondary to a coagulopathy. Activation of coagulation factors II, VII, IX, and X (the vitamin K–dependent factors) requires reduced vitamin K (hydroquinone) for posttranslational γ-carboxylation. Activation of these factors leads to oxidation of reduced vitamin K to inactive epoxide. The enzyme vitamin K reductase catalyzes the conversion of inactive epoxide back to active hydroquinone. Anticoagulation rodenticides antagonize the action of vitamin K epoxide reductase, so levels of hydroquinone decrease. Activation of the vitamin K–dependent coagulation factors cannot occur (Figure 82-1) and levels of active factors II, VII, IX, and X decrease. Depleted levels of these factors will result in a coagulopathy and associated clinical signs. Coagulopathies typically are characterized by lung and body cavity bleeding, but bleeding at other sites such as the joints and trachea have been reported. Potentially fatal hemorrhage in the central nervous system (CNS) is always possible.

82.3.2 Case Management

82.3.2.1 Acute Ingestion

Animals will most commonly present to the emergency clinician following a recent witnessed ingestion of rodenticide. The most common anticoagulants described in a retrospective study are brodifacoum (80%), diphacinone (18.7%), and chlorophacinone (2.7%).[2] If a patient presents within 4 hours of ingestion and there is no contraindication to emesis (seizures, depression) then this should be implemented immediately with apomorphine or hydrogen peroxide (dogs). Cats are preferably given xylazine for induction of emesis. Activated charcoal should also be administered to adsorb remaining rodenticide in the gastrointestinal (GI) tract. Dogs that ingest rodenticide typically are not fastidious eaters and will likely eat a charcoal and dog food slurry mix. Sodium sulfate (250 mg/kg in dogs and cats) or a 70% sorbitol solution (1 to 2 ml/kg) may be administered as a cathartic (see Chapter 77, Approach to Poisoning and Drug Overdose).

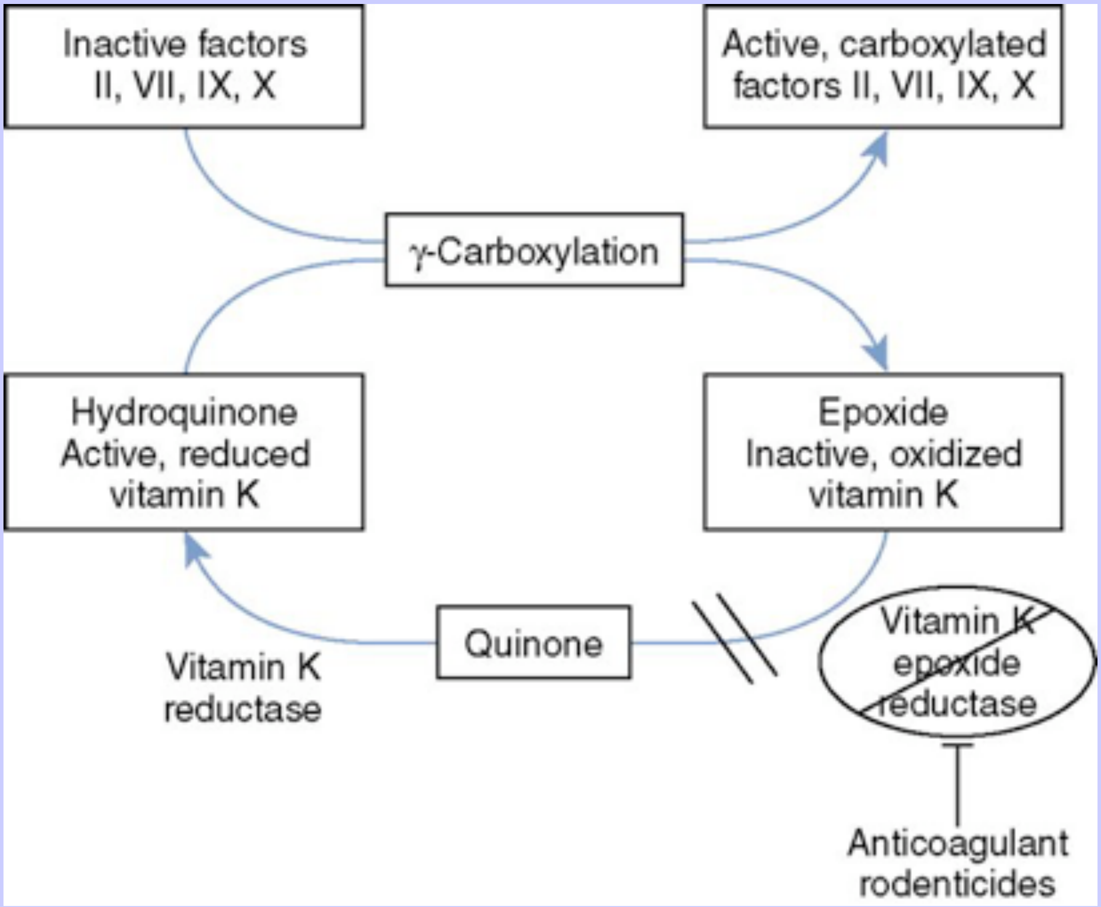
A prothrombin time (PT) should be obtained for all patients 48 hours after ingestion. The PT is a measure of the extrinsic pathway, including factor VII. Factor VII has the shortest half-life of all the vitamin K_1–dependent coagulation factors (6.2 hours), and as a result the PT will be prolonged before the activated partial thromboplastin time (aPTT) and before the development of clinical signs. Forty-eight hours is sufficient time for factor VII levels to be depleted, resulting in a prolongation of the PT, but not enough time for depletion of 346 the other factors that would result in clinical bleeding. If the PT is prolonged 48 hours after ingestion, oral 347 vitamin K (also known as phytonadione) should be started at a dosage of 2.5 mg/kg pO q12h. Most anticoagulant rodenticides are now second-generation[2] products, and treatment should therefore be continued for 4 weeks. Forty-eight hours after the last dose of vitamin K, a PT should be rechecked to ensure that an adequate course of therapy has been given. If the PT is still prolonged, vitamin K therapy should be continued for an additional 1 to 2 months. One other option is to treat empirically with vitamin K_1 for 4 weeks and then check the PT 48 hours after the last dose. Because of the cost of vitamin K_1, checking the PT 48 hours after ingestion generally is preferred.

Table 82-1 Mechanism of Action, Pathologic Consequences, and Lethal Dose of Rodenticides

Rodenticide	Class	Mechanism of Action	Pathologic Consequences	Lethal Dose (mg/kg)	
				Dog	**Cat**
Brodifacoum	Second-generation hydroxycoumarin	Inhibition of vitamin K epoxide reductase	Clinical bleeding due to coagulopathy	0.2 to 4	25
Bromadiolone	Second-generation hydroxycoumarin	Inhibition of vitamin K epoxide reductase	Clinical bleeding due to coagulopathy	11 to 15	25
Chlorophacinone	Indandione	Inhibition of vitamin K epoxide reductase	Clinical bleeding due to coagulopathy	NK	NK
Diphacinone	Indandione	Inhibition of vitamin K epoxide reductase	Clinical bleeding due to coagulopathy	0.9 to 8	15
Warfarin	First-generation hydroxycoumarin	Inhibition of vitamin K epoxide reductase	Clinical bleeding due to coagulopathy	20 to 300	5 to 30
Cholecalciferol	Cholecalciferol	Increased gastrointestinal absorption and decreased renal calcium loss	Hypercalcemia leading to acute renal failure	1.5 to 8	NK
Bromethalin	Bromethalin	Uncoupling of oxidative phosphorylation	Neurologic signs from intramyelinic edema	2.5 to 5	0.5 to 1.5

NK, Not known.

Figure 82-1 Mechanism of action of anticoagulant rodenticides.


Inactive factors II, VII, IX, X
Active, carboxylated factors II, VII, IX, X
γ-Carboxylation
Hydroquinone Active, reduced vitamin K
Epoxide Inactive, oxidized vitamin K
Quinone
Vitamin K reductase
Vitamin K epoxide reductase
Anticoagulant rodenticides

82.3.2.2

Coagulopathies

If the patient has evidence of clinical bleeding, presenting complaints may include lethargy, anorexia, dyspnea, hemoptysis, and/or lameness.[3] Physical examination will typically show abnormalities consistent with the location of the bleed. Auscultation may reveal dull lung sounds if there is pleural effusion, or dull heart sounds due to pericardial effusion. Episcleral hemorrhage or subcutaneous hematomas may also be seen. Palpation of the abdomen, kidneys, or joints may be painful. Differential diagnoses for animals with a severe coagulopathy include anticoagulant rodenticide intoxication, disseminated intravascular coagulation (secondary to the systemic inflammatory response), severe thrombocytopenia, hemophilia, and liver failure.

A minimum database may be consistent with acute hemorrhage (low total solids with low or normal packed cell volume). Blood gas analysis may reveal a metabolic acidosis (rule out increased lactate secondary to decreased perfusion) and an elevated alveolar-arteriolar gradient if there is pleural or parenchymal hemorrhage. A blood smear should be evaluated for erythrocyte morphology and adequacy of platelets. Patients with anticoagulant rodenticide intoxication are often severely thrombocytopenic; this is thought to be a result of profound consumption secondary to the massive hemorrhage that can occur. Every patient with evidence of severe bleeding should be evaluated for objective measures of coagulation.

Anticoagulant rodenticides will induce a prolongation of the PT before the aPTT. The aPTT will become prolonged as factors II, IX, and X are depleted and from consumption of other factors once bleeding has occurred. The activated clotting time also reflects the intrinsic pathway and will therefore not be prolonged until factor depletion is severe. If a patient has a greater elevation in the PT relative to the increase in aPTT, then anticoagulant rodenticide intoxication is likely. Similarly, anticoagulant rodenticide intoxication is unlikely in a patient with a severe prolongation of the aPTT and a mild prolongation of the PT. If both the PT and the aPTT are severely prolonged, then a diagnosis of anticoagulant rodenticide intoxication is more difficult.

The PIVKA (proteins induced by vitamin K antagonism) was previously thought to be a more specific test for diagnosing anticoagulant rodenticide intoxication. However, it can be elevated with other disease processes, particularly severe liver disease and/or malabsorption and maldigestion syndromes. One study found that 347
performing a PT and a PIVKA simultaneously added no additional diagnostic information.[4] Definitive 348
diagnosis is possible with anticoagulation rodenticide screens utilizing spectrophotometry (available at veterinary laboratories), which can quantitatively demonstrate the presence of the toxin in whole blood. The concentration of rodenticide detected does not correspond with the severity of the change in PT, aPTT, or platelets.[2] Although it takes 3 to 5 days to obtain results of this screen, the clinician can obtain a definitive diagnosis of anticoagulant rodenticide intoxication and learn the type of rodenticide ingested. This is especially useful when the owner is adamant that there has been no exposure to rodenticide. Unless the patient is receiving Coumadin therapeutically, there is no possibility of a false-positive test result.

Radiography may reveal loss of body cavity detail, and effusion may be seen on thoracic and abdominal ultrasonography. If no pleural hemorrhage is present, a patchy to diffuse pulmonary alveolar to interstitial pattern consistent with alveolar hemorrhage may be noted.

Treatment of the symptomatic patient is based on correcting the coagulopathy, providing exogenous vitamin K_1 for regeneration of coagulation factors, and supportive care. Clotting factors in the form of fresh frozen plasma (typically 10 to 20 ml/kg) or fresh whole blood should be administered to the patient until clotting times have normalized and the hematocrit is greater than 24%. Dyspneic patients will require oxygen therapy, and the hemorrhagic pleural effusion may become so severe that they require thoracentesis. This ideally should be performed after correction of the coagulopathy, but will depend ultimately on the clinical status of the animal. Pericardiocentesis may also become necessary in animals with hemorrhagic pericardial effusion, but only in extremely critical cases. Exogenous vitamin K_1 should be administered at an initial dosage of 5 mg/kg SC using a small-gauge needle. There is a high frequency of anaphylaxis following intravenous administration of vitamin K_1, so this route is not recommended. There is better bioavailability of vitamin K_1 when ingested, so therapy should be switched from subcutaneous to the oral route as soon as possible. Oral vitamin K should be administered at 2.5 mg/kg PO with food q12h for 4 weeks, and a recheck PT performed 48 hours following cessation of therapy (as described earlier in the section Acute Ingestion). Supportive care, including correcting the anemia and supplying oxygen therapy, will be necessary while the blood is resorbed and clinical signs resolve. 348

82.3.3 Outcome

Patients with a witnessed anticoagulant rodenticide ingestion that are rapidly treated by induction of emesis, activated charcoal, and a PT performed 48 hours after ingestion have an excellent prognosis. Those patients with a severe coagulopathy and clinical evidence of bleeding also carry an excellent prognosis when treated aggressively and appropriately.[2,5] Of all the causes of a coagulopathy, anticoagulant rodenticide intoxication has the best prognosis. In an abstract, 98.6% (74 of 75) of dogs that had a positive anticoagulant rodenticide screen survived,[2] emphasizing the importance of a timely and accurate diagnosis and treatment.

82.4 CHOLECALCIFEROL

82.4.1 Pathophysiology and Clinical Signs

Intoxication from cholecalciferol rodenticide results in hypercalcemia and associated clinical signs. Following ingestion of the bait, cholecalciferol (vitamin D_3) is rapidly absorbed and transported to the liver by specific binding proteins. It is first converted within the hepatocytes to 25-hydroxycholecalciferol and then to 1,25-dihydroxycholecalciferol within the kidney, which increases GI absorption of calcium, reduces renal excretion of calcium, and increases resorption of calcium from the bone. The primary pathologic effects of the hypercalcemia are acute renal failure and cardiac arrhythmias (see Chapter 56, Calcium Disorders).

Clinical signs can develop between 4 and 36 hours after ingestion. Initial signs are related to the hypercalcemia, and include polyuria and polydipsia (through inhibition of ADH), lethargy, anorexia, and vomiting. Acute renal failure develops secondary to the hypercalcemia. Dehydration quickly ensues because of decreased fluid intake and increased GI and renal losses. Cardiac arrhythmias will often be present because of mineralization of the heart or changes in the ratio of intracellular-to-extracellular ion concentrations and an increase in the depolarization threshold.

82.4.2 Case Management

82.4.2.1 Acute Ingestion

Many patients present for treatment following recent witnessed ingestion of the rodenticide. As with acute anticoagulant ingestion, GI decontamination strategies should be performed unless there is a contraindication to doing so (see Chapter 77, Approach to Poisoning and Drug Overdose). A serum calcium level should be checked 48 hours after acute ingestion.

82.4.2.2 Hypercalcemia

In patients with hypercalcemia, cholecalciferol intoxication should always be considered and owners questioned accordingly. Other differential diagnoses for increased ionized calcium levels include hypercalcemia of malignancy, hypoadrenocorticism, chronic renal failure, primary hyperparathyroidism, osteolytic bone disease, and ingestion of vitamin D ointments (psoriasis creams) or supplements. Physical examination may reveal depression, weakness, dehydration, and cardiac arrhythmias. Blood work will reveal severe hypercalcemia (total and ionized), and hyperphosphatemia. As the toxicosis progresses, hyperproteinemia, azotemia, hyperkalemia, and metabolic acidosis may also develop. Histopathology commonly reveals diffuse soft tissue mineralization.

Therapy for hypercalcemic patients is directed toward reducing blood calcium levels and preventing acute renal failure. Intravenous isotonic saline (0.9% NaCl) should be administered to correct dehydration and provide moderate volume expansion. The high sodium concentration of 0.9% NaCl (154 mEq/L) will induce a calciuresis. Renal calcium loss will also be enhanced by furosemide, glucocorticoids, and salmon calcitonin.[6] However, furosemide should be administered only after fluid deficits are corrected and glucocorticoids given only after other diagnoses of hypercalcemia have been excluded. In addition to inducing a calciuresis, salmon calcitonin inhibits osteoclast activity and thus reduces the resorption of calcium from bones. However, there is a risk of anaphylaxis with salmon calcitonin therapy. Pamidronate disodium is a bisphosphonate that also inhibits osteoclastic bone resorption and reduces calcium concentrations within 48 hours of administration (see Chapters 56 and 135, Calcium Disorders and Acute Renal Failure, respectively).

82.4.3 Outcome

Dogs with cholecalciferol intoxication and mild to no azotemia have a fair to good prognosis with aggressive medical therapy; in four published case reports, four out of six dogs survived.[6–9] Three cats with hypercalcemia associated with cholecalciferol toxicity were reported to have survived in one published case series.[10] Once hypercalcemia and acute renal failure have developed, prognosis is poor. Rapid and aggressive therapy to reduce the calcium concentration and prevent soft tissue mineralization will lead to a better chance of survival.

82.5 BROMETHALIN

82.5.1 Pathophysiology and Clinical Signs

The toxic effects of bromethalin are due to the uncoupling of oxidative phosphorylation with a resultant decrease in adenosine triphosphate (ATP) production. This decrease in cellular energy will lead to an inability of the ATP-dependent membrane transport pumps to function. The nonfunctioning Na^+,K^+-ATPase transport pump will lead to a buildup of intracellular sodium, which will cause water to move into the cell. Cells of many organs can be affected, but clinical signs are predominantly associated with cerebral edema and the resultant elevated intracranial pressure.

Clinical signs and their onset vary with the dose ingested. Ingestion of doses larger than the LD_{50} (the dose of the drug that will cause death in 50% of experimental animals; dogs 4.7 mg/kg and cats 1.8 mg/kg) results in severe muscle tremors, hyperthermia, extreme hyperexcitability, and focal or generalized seizures within 24 hours. Clinical signs with lower doses may manifest between 1 and 3 days; signs include hind limb ataxia, paresis or paralysis, and CNS depression.

82.5.2 Case Management

82.5.2.1 Acute Ingestion

Animals that are presented following acute ingestion require immediate and aggressive decontamination. This will include emesis induction or general anesthesia, intubation, and gastric lavage if the patient is unable to protect its airway and is at risk of aspiration. Repeated doses of activated charcoal should be administered (3 to 5 g/kg q6-8h) for 48 hours because of enterohepatic circulation of the toxin. Sodium sulfate (250 mg/kg in dogs and cats) or a 70% sorbitol solution (1 to 2 ml/kg) may be administered as a cathartic (see Chapter 77, Approach to Poisoning and Drug Overdose).

82.5.2.2 Neurologic Complications

Treatment of animals with neurologic signs is based on seizure control and supportive care. Attempts to maintain cerebral perfusion pressure and oxygen delivery should be made. These strategies include the administration of mannitol to reduce cerebral edema, elevation of the head at a 15-degree to 30-degree incline, prevention of jugular compression, and maintenance of normocapnia. Strategies to ensure normoglycemia and prevent hyperthermia should also be considered. Treatment of bromethalin-induced neurologic signs with glucocorticoids has commonly been cited.[11] However, there is no evidence supporting this recommendation. Considering the known side effects of steroids, including hyperglycemia, and only a theoretical benefit, glucocorticoid use in animals with bromethalin intoxication cannot be recommended.

Unfortunately, a definitive diagnosis can be made only postmortem. Histopathologic examination of the cerebrum, cerebellum, brainstem, and spinal cord may support a diagnosis of bromethalin intoxication. Diffuse white matter vacuolation (spongy degeneration) with microgliosis is described consistently.[12] Gas chromatography with electron capture can be used to detect bromethalin in samples of kidney, liver, fat, or brain.

82.5.3 Outcome

Animals with severe signs have a very poor prognosis. To the authors' knowledge, there are no reports of dogs ingesting more than 5 mg/kg bromethalin, developing neurologic signs, and surviving. However, there is a report of a dog that survived after ingesting a lower dose of bromethalin (<2.5 mg/kg), which led to tremors, ataxia, and muscle weakness.[13] GI decontamination with induction of emesis and repeated doses of activated charcoal to prevent signs is therefore essential to patient survival.[11]

82.6 MISCELLANEOUS RODENTICIDES

Zinc phosphide is a restricted use pesticide, and companion animal intoxication is therefore rare. However, commercial use is increasing and secondary intoxication of dogs (from ingestion of poisoned rodents) is possible.[14] Following ingestion and contact with gastric acid, zinc phosphide is hydrolyzed to phosphine gas and free radicals. Enhanced susceptibility to zinc phosphide occurs when it is ingested with food because of gastric acid secretion. The kinetics for hydrolysis are favored at a lower pH, and the rate of phosphine gas generated is markedly enhanced. The mechanism of action is not fully understood, but it has been proposed that free radicals such as reactive oxygen species produced by phosphine are responsible for the toxicity in mammals. The onset of clinical signs is variable but is usually evident 15 minutes to 4 hours following ingestion of a toxic dose. Death usually occurs in 3 to 48 hours. Clinical signs include lethargy, vomiting, and rapid, stertorous breathing. Clinical signs of ataxia, weakness, gasping, convulsions, and hyperesthesia may be seen. The unpleasant odor of phosphine (smells like acetylene, garlic, or rotting fish) may be detectable on the breath, vomitus, or carcass. No specific antidote exists, and treatment is based on decontamination and supportive care.

Twenty-five years ago, strychnine was commonly used as a rodenticide, and accidental or malicious intoxication occurred frequently. It is now a restricted use pesticide and canine or feline exposure is rare, although secondary intoxication is more likely to occur than with zinc phosphide. Strychnine prevents the uptake of glycine at inhibitory synapses of Renshaw cells in the CNS. This inhibition of an inhibitory pathway is termed *disinhibition* and results in a net excitatory effect from an excessive afferent input and efferent response. Onset of stimulant activity, including apprehension and muscle contractions, occurs within minutes to hours of ingestion. Signs progress to convulsions, extensor rigidity, and death. Confirmation of strychnine exposure can be made from 349 350 stomach contents or postmortem tissue samples.[15] Decontamination strategies are recommended unless clinical signs are apparent. Therapy to prevent seizures and provide muscle relaxation and supportive care should be instituted. Animals often die from respiratory muscle paralysis and hypoventilation; mechanical ventilation of the paralyzed patient may therefore prove lifesaving.

82.7 Suggested Additional Readings*

1. MJ Murphy: Rodenticides. *Vet Clin Am Small Anim Pract*. **32**, 2002, 469, *The most comprehensive and complete review of rodenticides in the veterinary literature*.

2. EA Rozanski, KJ Drobatz, D Hughes, et al.: Thrombotest (PIVKA) test results in 25 dogs with acquired and hereditary coagulopathies. *J Vet Emerg Crit Care*. **9**, 1999, 73, *A report of PIVKA test results, as well as PT and aPTT results, in bleeding dogs*.

3. LS Waddell, RH Poppenga, KJ Drobatz: Anticoagulant rodenticide screening in dogs and cats: 137 cases (1996–2003). *J Vet Emerg Crit Care*. **13**, 2003, 168,(abstract) *Retrospective study describing clinical signs, clinicopathologic data, and outcome in 137 patients that had an antemortem blood sample submitted for an anticoagulant rodenticide screen*.

* See the CD-ROM for a complete list of references

83 Chapter 83 Sedatives, Muscle Relaxants, and Opioids Toxicity

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83.1 KEY POINTS

- Overdose with sedatives causes primarily a dose-dependent central nervous system (CNS) depression.
- Signs of acute toxicity with muscle relaxants are often an amplification of their main therapeutic effects: muscular flaccidity, CNS and respiratory depression, and anticholinergic syndrome.
- Opioid overdose may alter mental status, cause respiratory depression, and produce miosis in dogs and mydriasis in cats.
- Sedatives, muscle relaxants, and opioids undergo hepatic biotransformation, with primary excretion of their metabolites in the urine. Thus, the metabolism of these drugs may be impaired in patients with hepatic disease or renal impairment, increasing the duration and intensity of their pharmacologic action.
- Treatment of intoxication with sedatives, muscle relaxants, and opioids is based on general supportive measures. Antidotes are available for only the benzodiazepines, α_2-agonists, and opioids.

83.2 INTRODUCTION

Dogs and cats may experience toxicity from sedatives, central muscle relaxants, and opioids, either by iatrogenic overdose by a veterinary health care provider or by consumption of the owner's medications. All of the agents discussed in this chapter are dispensed only by prescription, and several are not approved for use in veterinary species. Differential diagnoses to consider include the ingestion of other neurotoxins and drugs, as well as primary central nervous system (CNS) disorders. Blood and urine concentration of many of these drugs can be measured. The clinical picture and treatment of overdose for each of these drug categories will be discussed separately.

83.3 SEDATIVE OVERDOSE

Sedatives include a variety of agents that have the capacity to depress the function of the CNS and result in sedation. They may also contain muscle relaxant, anxiolytic, and anticonvulsant properties. Some euthanasia solutions are formulated with highly concentrated barbiturate products, and acute intoxication with these agents may occur after ingestion of meat from an animal recently euthanized (relay toxicosis). It is important to consider that studies of clinical use or toxicity for several of the drugs discussed in this section have been done only in humans.[1–4] Hence, it is unknown if the pharmacokinetics and clinical signs of overdose reported for individual agents would be different in veterinary species.

83.3.1 Mechanism of Action

The sedative agents have various modes of action that are summarized in Table 83-1.[1–4]

83.3.2 Pharmacokinetics

Table 83-2 describes the pharmacokinetics of the agents listed in Table 83-1.[1–8] All of these sedatives undergo hepatic biotransformation, with excretion of metabolites primarily in the urine. As a result, their metabolism may be impaired in patients with hepatic disease, and their metabolites may accumulate in patients with renal impairment. Benzodiazepines require significant hepatic microsomal enzyme metabolism, and barbiturates stimulate the hepatic microsomal enzyme system.

Table 83-1 Mechanism of Action of Sedatives[1-14]

Generic Name	Brand Name	Mechanism of Action
Benzodiazepines		
Alprazolam	Xanax	Benzodiazepine receptors are located on the $GABA_A$-receptor complex, a chloride ion channel in the brain and spinal cord. Their activation promotes binding of GABA to its receptor, thereby enhancing chloride currents through these channels (by increasing the frequency of channel openings). The cell membrane becomes hyperpolarized and resistant to excitatory stimuli, explaining the sedative, anticonvulsant, and muscle relaxant effects of benzodiazepines.
Clorazepate	Tranxene	
Chlordiazepoxide	Librium	
Clonazepam	Klonopin	
Diazepam	Valium	
Estazolam	ProSom	
Flurazepam	Dalmane	
Lorazepam	Ativan	
Midazolam	Versed	
Oxazepam	Serax	
Quazepam	Doral	
Temazepam	Restoril	
Triazolam	Halcion	
Imidazopyridines		
Zolpidem	Ambien	Modulates $GABA_A$-receptor chloride channel macromolecular complex.
Pyrazolopyrimidines		
Zaleplon	Sonata	Modulates $GABA_A$-receptor chloride channel macromolecular complex.
Phenothiazines		
Acepromazine	Atravet	Blocks postsynaptic dopamine and α_1-adrenergic receptors.
α_2-Agonists		
Medetomidine	Domitor	α_2-Adrenoreceptor agonists.
Xylazine	Rompun	
Barbiturates		
Phenobarbital	Luminal	Augment GABA responses by promoting the binding of GABA to its receptor $GABA_A$ and by increasing the length of time that chloride channels are open, and also opens the chloride channels in the absence of GABA at higher doses.
Pentobarbital	Nembutal	

GABA, γ-Aminobutyric acid.

83.3.3 Clinical Signs

For most sedative overdoses, the clinical picture is nonspecific. All of these drugs cause progressive CNS depression in proportion to the quantity of the agent consumed. Also, concurrent administration or ingestion of other CNS depressants (opioids, anesthetics) will have compounding effects. CNS sign vary from mental depression, ataxia, stupor, and surgical anesthesia, to coma. Finally, death will occur with sufficient depression of medullary neurons to disrupt coordination of cardiovascular function and respiration. Phenothiazines block α-adrenergic receptors and, if given concurrently with epinephrine, the β-activity will prevail, causing vasodilation and an increased heart rate. Clinical signs of overdoses with sedatives and possible interactions with various medications are summarized in Table 83-3.[1,3,7,9,10]

Table 83-2 Pharmacokinetics of Sedatives[12-18]

Generic Name	**Route**	**Half-life (hr)**	**LD_{50}**
Benzodiazepines			
Alprazolam	PO	12 ± 2	—
Clorazepate	PO	2.0 ± 0.9	—
Chlordiazepoxide	PO, IV, IM	10 ± 3.4	—
Clonazepam	PO	23 ± 5	—
Diazepam	PO, IV, IM, PR	2.5-2.3	20 mg/kg (dog)
Estazolam	PO	10-24	—
Flurazepam	PO	74 ± 24	—
Lorazepam	PO, IV, IM	14 ± 5	—
Midazolam	IV, IM	1.9 ± 0.6	IV: 1600 mg/kg
Oxazepam	PO	8.0 ± 2.4	—
Quazepam	PO	39	—
Temazepam	PO	11 ± 6	—
Triazolam	PO	2.9 ± 1.0	—
Imidazopyridines			
Zolpidem	PO	2.6	—
Pyrazolopyrimidines			
Zaleplon	PO	1.0	—
Phenothiazines			
Acepromazine	PO, IV, IM, SC	3	PO: 257 mg/kg IV: 61 mg/kg (mice)
α_2-Agonists			
Medetomidine	IV, IM	0.96 ± 0.25	80 mg/kg (rat)
Xylazine	IV, IM, SC	0.5	—
Barbiturates			
Phenobarbital	PO, IV	48	PO: 150 mg/kg IV: 83 mg/kg (rat)
Pentobarbital	PO, IV, IM, PR	8	PO: 85 mg/kg IV: 50 mg/kg (dog)

IM, Intramuscular; *IV,* intravenous; *LD_{50}*, lethal dose; *PO,* per os; *PR,* per rectum; *SC,* subcutaneous.

83.3.4 Treatment

Treatment of intoxications with sedatives is based on general supportive measures. Antidotes are available only for benzodiazepines and α_2-agonists. Decontamination should be performed as described in Chapter 77, Approach to Poisoning and Drug Overdose, if oral ingestion of a toxic dosage is suspected. Table 83-4 describes the treatment for each class of drugs.[1,3,11] In patients with severe mental depression, oxygen should be administered and a patent airway maintained to prevent aspiration pneumonia, hypercarbia, or hypoxemia. Mechanical ventilation should be initiated when indicated. Continuous electrocardiographic and blood pressure monitoring is required for patients manifesting cardiovascular instability. Intravenous crystalloid fluids should be administered to promote diuresis and therefore hasten the elimination of the metabolites of each of these drugs. Hypotension should be managed initially with intravenous fluids, followed by vasopressors if required. Seizures should be controlled with standard anticonvulsants. The patient's body temperature requires regular monitoring and appropriate measures must be taken to maintain euthermia. Aggressive supportive and nursing care will help prevent complications in recumbent animals.

Table 83-3 Clinical Signs of Toxicity of Sedatives and Potential Drug Interactions[1,3,7,9,10]

Drug Class	Clinical Signs of Toxicity	Drug Interactions
Benzodiazepines	Toxicity of these drugs is low CNS depression, ataxia and, uncommonly, respiratory depression and hypotension may occur Cats may develop hepatic failure after oral administration of diazepam	Cimetidine, fluoxetine, erythromycin, isoniazid, ketoconazole, propranolol, metoprolol, valproic acid: may inhibit the metabolism of benzodiazepines and cause excessive sedation
Imidazopyridines	CNS depression, ataxia, respiratory depression, pulmonary edema	
Pyrazolopyrimidines	CNS depression, ataxia, respiratory depression	
Phenothiazines	CNS depression, vasodilation, bradycardia, hypotension, pulmonary edema, seizure	Decrease dosage of general anesthetics Epinephrine reversal
α_2-Agonists	CNS depression, bradycardia, atrioventricular blocks, decreased myocardial contractility, decreased cardiac output, initially arterial hypertension followed by hypotension, decreased respiratory rate, apnea, cyanosis, vomiting, recurrence of sedation after initial recovery, occasional spontaneous muscle contractions (twitching), hypothermia, hyperglycemia, death from circulatory failure with severe pulmonary congestion, increased hepatic or renal enzymes	Decrease dosage of general anesthetics Concurrent use of epinephrine may induce ventricular arrhythmias
Barbiturates	Progressive CNS depression: stupor to coma, ataxia, respiratory depression, hypotension, decreased cardiac contractility, noncardiogenic pulmonary edema, aspiration pneumonia, renal failure, hypothermia, decreased GI motility, anemia, hypoglycemia Cats particularly sensitive to respiratory depressant effects	Accelerate the clearance of other drugs metabolized via hepatic microsomal enzymes Chloramphenicol may increase clinical effects

CNS, Central nervous system; *GI,* gastrointestinal.

Table 83-4 Treatment of Sedative Overdoses[1,3,11]

Drug	Management
Benzodiazepines Imidazopyridines	Flumazenil (Romazicon) is a benzodiazepine antagonist binding with high affinity to specific sites on the $GABA_A$-receptor, where it competitively antagonizes benzodiazepines binding and allosteric effects. It can also reverse effects of imidazopyridines and pyrazolopyrimidines.
Pyrazolopyrimidines	Flumazenil has a higher clearance and shorter elimination half-life (1 hr) than all clinically used benzodiazepine agonists. Recurrent benzodiazepine toxicity or resedation is therefore likely once the effects of flumazenil have worn off, and repeated administration may be necessary. Flumazenil is administered only by rapid IV injection because it is highly irritating, and care should be taken to avoid extravasation. Dosage: 0.05 mg/kg IV. Elimination is not enhanced by hemodialysis or hemoperfusion.
α_2-Agonists	Atipamezole (Antisedan) is an α_2-adrenergic antagonist that selectively and competitively inhibits α_2-adrenergic receptors, causing sympathetic outflow to be enhanced. It can reverse effects of medetomidine and xylazine. The onset of arousal is usually apparent within 5 to 10 minutes of intramuscular injection, depending on the depth and duration of sedation. Atipamezole will also produce a rapid improvement of bradycardia and respiratory depression. Atropine or glycopyrrolate should not be used to prevent or manage bradycardia, because tachycardia and hypertension may result. Atipamezole should be administered intramuscularly regardless of the route used for the α_2-agonist. The dosage is calculated based upon body surface area: 1 mg/m^2, or give IM an equal volume of atipamezole hydrochloride (Antisedan) and medetomidine (Dormitor) (ml per ml). Yohimbine or tolazoline can also be used to reverse the effects of xylaxine but are less specific antagonists with more side effects than atipamezole.
Barbiturates	Promote diuresis to increase the urinary flow rate. Also, alkalinizing the urine (pH >7) by intravenous administration of sodium bicarbonate will enhance the rate of excretion of unchanged drug in its ionized form. Hemodialysis and hemoperfusion can be used to maximize barbiturate elimination.

GABA, γ-Aminobutyric acid; *IV,* intravenous.

83.4

MUSCLE RELAXANTS OVERDOSE

Muscle relaxants reduce skeletal muscle tension without abolishing voluntary motor control. Effects occur at various levels of the CNS for most of the drugs, but some also act directly within the muscle. This clinical grouping of therapeutic agents accommodates a heterogeneous assembly of medications (Table 83-5) that differ in their chemical, pharmacologic, pharmacokinetic, and toxicologic properties. As a result, the type and severity of clinical effects after an overdose may be diverse. A number of agents are used to alleviate skeletal muscle spasms in human patients, but little is known about their clinical application in veterinary medicine. Neuromuscular blockers are muscle relaxants as well, but are discussed in Chapter 183 (Neuromuscular Blockers), Benzodiazepines were discussed in the previous section (Sedative Overdose).

83.4.1

Mechanism of Action

The mechanism of action of many of the neuromuscular blocking drugs is not well defined, but may be related in part to the sedative effects. Table 83-5 summarizes the skeletal muscle relaxants of clinical and toxicologic importance and their modes of action.[3,12–18]

83.4.2

Pharmacokinetics

A detailed discussion of muscle relaxant pharmacokinetics is beyond the scope of this chapter. The reader is encouraged to consult aforementioned references for further information.[3,12–19] It is important to recognize that limited pharmacokinetic data are available for many of these drugs in veterinary species, and thus elimination in dogs and cats may be unpredictable. In humans, most muscle relaxants have peak absorption within 1 to 6 hours and are distributed throughout the body. Therefore clinical effects are seen rapidly after ingestion. All of the muscle relaxants are metabolized in the liver, and their metabolites are eliminated mostly in the urine.[12]

83.4.3

Clinical Signs

In most cases of muscle relaxant overdose, the clinical features are exaggerations of their main therapeutic effects. Muscular flaccidity, CNS and respiratory depression, and an anticholinergic syndrome from the agents with antimuscarinic effects are often seen in acute toxicity. Additive sedation may occur when given with other CNS depressant agents. In the veterinary literature, only a few reports are available to describe the clinical course seen with muscle relaxants. Table 83-6 summarizes the clinical signs of acute toxicity with muscle relaxants in humans and in veterinary species.[3,12,14–16,20–23]

Table 83-5 Summary of Muscle Relaxants and Their Mechanisms of Action[3,12–18]

Generic Name	Trade Name	Site of Action	Mechanism of Action
Baclofen	Lioresal	CNS	$GABA_B$-agonist
Carisoprodol	Soma	CNS	Indirect GABA-agonist
Cyclobenzaprine	Flexeril	CNS	Tricyclic analog: decreases amplitude of monosynaptic reflex potentials by inhibiting descending serotonergic systems in spinal cord
Chlorzoxazone	Parafon Forte	CNS	Exact mechanism unknown; sedation
Dantrolene	Dantrium	Peripheral	Blocks calcium liberation from sarcoplasmic reticulum of skeletal muscle by binding to ryanodine receptor
Methocarbamol	Robaxin	CNS	Unknown; structurally related to guaifenesin
Metaxalone	Skelaxin	CNS	Not established; thought to be related to its sedative properties
Orphenadrine	Norflex	CNS	Directly causes dopamine release; NMDA receptor antagonist; blocks norepinephrine uptake; peripheral antimuscarinic action
Tizanidine	Zanaflex	CNS	Central α_2-adrenergic agonist

CNS, Central nervous system; *GABA,* γ-aminobutyric acid; *NMDA,* N-methyl-D-aspartic acid.

83.4.4

Treatment

Because of the potential for a rapid onset of clinical signs, decontamination should be attempted without delay. General guidelines for decontamination can be found in Chapter 77, Approach to Poisoning and Drug Overdose. For baclofen and carisoprodol, only one dose of activated charcoal with a cathartic is necessary, because these drugs do not undergo enterohepatic circulation. For the remaining muscle relaxants, efficacy of multidose activated charcoal regimens has not been established.[12] Gastric lavage should be performed in cases of large ingestions, and it is important that the anesthetic protocol used does not compound the CNS depression. A short-acting induction agent such as propofol, followed by inhalant anesthesia, is recommended. The airway must be protected at all times with a cuffed endotracheal tube.

Because there is no antidote for centrally acting muscle relaxant overdose, aggressive supportive care and intensive monitoring are imperative. The patient's ventilation and oxygenation should be monitored closely. Endotracheal intubation and positive-pressure ventilation should be considered in select patients (see Chapter 213, Basic Mechanical Ventilation).

Table 83-6 Clinical Signs of Acute Muscle Relaxant Toxicity[3,6,12,14–16,20–23]

Drug	Clinical Signs
Baclofen	Vomiting, salivation, sedation, ataxia, vocalization, hypotension or hypertension, bradycardia, tachycardia, coma, dyspnea, respiratory arrest Deaths in dogs have occurred at doses between 8 and 16 mg/kg[14]
Carisoprodol	Coma, hypotension, seizure, shock, respiratory depression, pulmonary edema, respiratory arrest and eventually cardiac arrest, nystagmus, vomiting, urticaria, pruritus, ataxia, tremors, agitation, myoclonus, tachycardia
Cyclobenzaprine	Anticholinergic toxidrome, lethargy, sinus tachycardia, agitation, hypertension or hypotension
Chlorzoxazone	CNS depression, GI upset, hypotonia, areflexia, hypotension, hepatotoxicity
Dantrolene	Hypotonia, sedation, hepatotoxicity
Methocarbamol	Sedation, lethargy, weakness, ataxia, salivation, emesis
Metaxalone	Sedation, GI upset, hepatotoxicity, nephrotoxicity
Orphenadrine	Anticholinergic toxidrome, mydriasis, tachycardia, coma, seizures, hypothermia, shock, cardiac arrest

CNS, Central nervous system; *GABA,* γ-aminobutyric acid; *GI,* gastrointestinal.

Animals manifesting cardiovascular instability require continuous electrocardiographic and blood pressure monitoring. Bradycardia from baclofen toxicity was responsive to atropine in human patients.[20,24] Hypotension should be treated initially with intravenous crystalloid or colloid fluids (see Chapter 65, Shock Fluids and Fluid Challenge), followed by vasopressors if needed (see Chapter 176, Vasoactive Catecholamines). Hypertension should be treated with vasodilators (e.g., nitroprusside, amlodipine), if necessary (see Chapter 178, Antihypertensives). Because baclofen and carisoprodol are excreted by the kidneys, adequate diuresis is important. Also, hemodialysis or hemoperfusion will reduce the elimination half-life for carisoprodol.[12,20]

Agitation can be treated with benzodiazepines. Seizures require prompt treatment with standard anticonvulsants. However, if carisoprodol has been ingested, barbiturates are not recommended for seizure control because they may compound the CNS depression. Diazepam, despite also being a γ- aminobutyric acid agonist, is the drug of choice for baclofen and carisoprodol-induced seizures.[14–16,20] Flumazenil and physostigmine have been used to help reverse comatose states in cases of baclofen toxicosis in humans.[20,25] Flumazenil had varied results, because it may be a proconvulsant when combined with a potential γ-aminobutyric acid antagonist like baclofen.[20] Temperature regulation may be abnormal in recumbent or comatose patients; therefore close monitoring and heat support, if necessary, are recommended.

Table 83-7 Functions of Opioid Receptors

Opiate Receptor	Function
Mu	Analgesia
	Respiratory depression
	Euphoria
	Bradycardia
	Constipation
	Vomiting
	Physical dependence
Delta	Analgesia
Sigma	Autonomic stimulation
	Dysphoria
	Hallucinations
Kappa	Analgesia
	Sedation
Epsilon	Analgesia

83.4.5 Prognosis

Asymptomatic patients having ingested any of these drugs should be observed for a minimum of 24 hours. The prognosis for toxicity with most of these muscle relaxants in veterinary medicine is unknown. For symptomatic patients with baclofen toxicity, resolution of clinical signs may take several days in severe cases, but if adequate supportive care and monitoring are available, the prognosis is generally good.[14] The vast majority of human patients recover after prompt recognition of the toxic condition and rapid institution of supportive care.[26]

83.5 OPIOID OVERDOSE

Opioids have been the mainstay of pain management for thousands of years, and they remain so today in both human and veterinary medicine. They are drugs derived from opium, and they include the natural products morphine and codeine, as well as many synthetic derivatives such as heroin, hydrocodone, and hydromorphone.[27]

83.5.1 Mechanism of Action

Opioids produce their effects by interacting with specific receptors distributed throughout the central and peripheral nervous systems, the gastrointestinal (GI) tract, the urinary tract, and other smooth muscles.[27] Five receptors have been identified: mu (μ), kappa (κ), delta (δ), sigma (σ), and epsilon (ε), and each is associated with certain clinical effects, as described in Table 83-7.[3] Opioid receptor activation results in inhibition of adenyl cyclase activity, activation of receptor-operated potassium currents, and suppression of voltage-gated calcium currents. These effects cause hyperpolarization of the cell membrane, decreased neurotransmitter release and reduced pain transmission.[27]

Functionally, opioids can be classified into four groups: morphine-like opioid agonists, opioid antagonists, mixed agonist-antagonists, and partial agonists (see Chapter 184, Narcotic Agonists and Antagonists).

83.5.2 Pharmacokinetics

An in-depth discussion of opioid pharmacokinetics is beyond the scope of this chapter (see Chapter 184, Narcotic Agonists and Antagonists, and references).[3,27,28] However, several points need emphasis. Morphine, oxymorphone, hydromorphone, butorphanol, and buprenorphine are well absorbed after intravenous, intramuscular, subcutaneous, oral, and rectal administration. However, first-pass metabolism is significant and results in low bioavailability and a less predictable effect after oral ingestion.

Distribution of opioids from the blood to the CNS is variable. Generally, with the highly lipid-soluble drugs (heroin, codeine, fentanyl), onset of action occurs most rapidly, and resolution of the pharmacologic effects is faster. Drugs that are less lipid soluble, such as morphine, move less rapidly and therefore take longer to be effective and may have a longer duration of action. The clinical effects of most opioids persist for 2 to 8 hours; exceptions are fentanyl, which lasts for 15 minutes and methadone which persists for 24 to 48 hours.[3,27–29] All opioids are metabolized primarily in the liver via glucuronidation. Cats are deficient in this metabolic pathway, and therefore the half-life of certain drugs may be prolonged. Elimination is primarily renal.[3] Patients with severe hepatic and renal disease are theoretically at increased risk of toxicity because of the accumulation of active metabolites. In normal dogs, the lethal dose for morphine is 100 mg/kg.[3]

Opiate administration may obscure the clinical course and physical examination findings in some animals, and therefore should be used cautiously in patients with intracranial disease, increased intracranial pressure, acute respiratory dysfunction, and acute conditions of the abdomen. Opioids may lead to hypoventilation and hypercapnia, which cause cerebral vasodilation and increased intracranial pressure. In patients with respiratory dysfunction and decreased carbon dioxide sensitivity, opioid drug administration may exacerbate the hypercapnia, necessitating mechanical ventilation. Neonatal and geriatric patients are more susceptible to the effects of opioids and require lower dosages. In the developing fetus, opiates pass more easily into the CNS because the blood-brain barrier is not fully developed. Therefore a fetus may suffer severe depression while the mother has no evidence of side effects. Small amounts of opioids can also be distributed in the milk of nursing mothers.[27,28]

Opioids can interact with many drugs that might potentiate their effects. Morphine is contraindicated in human patients receiving monoamine oxidase inhibitors (MAOIs). Humans may exhibit signs of opiate overdose after receiving therapeutic doses of morphine while taking MAOIs.[3,30] Also, fentanyl, meperidine, tramadol, methadone, and dextromethorphan are weak serotonin reuptake inhibitors and have all been involved in serotonin toxicity reactions with MAOIs.[30] Interactions between other opioids and MAOIs have not been shown in dogs[31] (see Chapter 91, Serotonin Syndrome).

Phenothiazines potentiate opioids, possibly by interfering with their metabolism.[27] Cimetidine may increase opioid effects by increasing the duration of action. Erythromycin may also enhance opioid effects.[32]

83.5.3 Clinical Signs

The clinical signs seen with opioid overdose are caused by an amplification of their action at the receptors discussed earlier. The μ receptor, which mediates many of the life-threatening effects, including respiratory depression, is principally affected. There is a classic triad seen with opioid toxicity: CNS depression, respiratory depression, and miosis in dogs. Cats typically develop mydriasis. Multiple organ systems can also be affected. Patients may be hyporeflexic, hypothermic, hypotensive, and have decreased borborygmi. These toxic effects are mediated primarily through stimulation of the μ, κ, and δ receptors.[3,27,28] The miosis in dogs results from μ-related stimulation of the visceral nuclei of the oculomotor nuclear complex and the parasympathetic nerve that innervates the pupil.[33]

The patient's level of consciousness can vary from excitement to dysphoria and from mild sedation to coma. Profound CNS depression, impaired gag response, cough suppression, and centrally mediated nausea and vomiting place the animal at high risk for pulmonary aspiration of gastric contents.[3] Seizures can occur with high doses of agonist opioids. This is well recognized in humans[27]; however, its occurrence in small animals is unknown. Opioids may alter the thermoregulatory response. Hypothermia commonly is seen in dogs, whereas hyperthermia may occur in cats.[34]

The most significant adverse side effect of opioids is respiratory depression. It is caused by a reduction in responsiveness to carbon dioxide in the brainstem respiratory center, as well as the centers that regulate respiratory rhythm. Areas of the medulla oblongata that control ventilation (nucleus tractus solitarius and nucleus ambiguus) have many opioid binding sites, and these respiratory neurons are inhibited by opioid receptor agonists. Attenuation of normal chemoreceptor-mediated ventilatory responses to hypercapnia and hypoxia by opioids may also lead to ventilatory depression. Dogs and cats seem to be less sensitive than humans, in whom respiratory arrest is responsible for most opioid-related deaths.[3,27]

Initially, respiratory depression may be subtle in some patients, because small decreases in tidal volume may occur before the respiratory rate declines. With further progression, the rate, tidal volume, and minute volume all decrease. Therefore the rate alone can be an unreliable measure of ventilation. Because hypoventilation is defined as an inability of the respiratory apparatus to eliminate metabolically produced carbon dioxide, the finding of hypercarbia on arterial or venous blood gas analysis is the most objective determinant of the presence and degree of respiratory depression. Opioids may also indirectly induce panting in dogs by resetting the thermoregulatory center, so the animal attempts to lose heat by increasing the respiratory rate, despite a normal to low body temperature.

The effects of opioids on the cardiovascular system are minimal at therapeutic doses and even in cases of toxicity. Pure opioid agonist interaction with μ receptors may result in bradycardia and cardiac conduction abnormalities. The systemic vascular resistance remains relatively stable after opioid administration, although morphine may decrease peripheral vascular tone.[35] Morphine and meperidine, when given intravenously, may cause histamine release leading to peripheral dilation (arterial and venous) and bradycardia. Cutaneous signs include itching, warmth, and urticaria.[28]

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Opioids cause a variety of direct gastrointestinal (GI) effects. They decrease the tone of the lower esophageal sphincter. Intestinal tone is increased while propulsive activity is reduced. Opioids also lower small intestinal secretions (pancreatic, biliary, and electrolytes and fluid) and enhance intestinal fluid absorption. These actions may result in constipation. Morphine has been associated with spasm of the sphincter of Oddi; therefore it should not be used during treatment of obstructive biliary or pancreatic diseases in humans. In addition, opioids can directly stimulate the chemoreceptor triggering zone and thus may cause nausea and vomiting.[27] At high doses, opioids may increase ureteral tone, bladder tone, and external sphincter tone, leading to urinary retention. Morphine is reported to increase antidiuretic hormone release and thus reduce urine production and cause an increase in specific gravity.[28]

83.5.4 Treatment

The mainstays of therapy for opioid overdose include providing a means for adequate ventilation and the administration of naloxone, an opioid antagonist. Patients whose respiratory status is sufficiently compromised should be intubated and supported with 100% oxygen and positive-pressure ventilation while naloxone is administered. Mechanical ventilation with positive end-expiratory pressure may be required if there is no response to the naloxone or if adequate oxygenation and ventilation cannot be achieved (see Chapter 213, Basic Mechanical Ventilation). Intubation and cuff inflation provides optimal airway control, decreases the risk of aspiration if vomiting occurs, allows access for airway suctioning and institution of positive pressure ventilation, and enables the administration of naloxone via the endotracheal route if intravenous access cannot be obtained.

GI decontamination should be considered in patients who have had oral exposure to opioids, particularly those drugs that can have delayed absorption such as loperamide and sustained-release morphine products. Concomitant use of naloxone may facilitate GI decontamination by decreasing GI atony (increasing GI tone). Although they occur rarely, seizures, hypotension, and cardiac arrhythmias should be treated with standard therapies. Body temperature should be monitored and euthermia maintained.

Naloxone is a synthetic derivative of oxymorphone (see Chapter 184, Narcotic Agonists and Antagonists). It is the opioid antagonist of choice, because it competitively binds opioid receptors κ, δ and, particularly, μ. It has a greater affinity for receptors than do the agonists. It is highly lipophilic and moves rapidly into the CNS. Naloxone usually has an onset of action of 1 to 2 minutes when given intravenously. The duration of action usually persists from 45 to 90 minutes. The dosage of naloxone for dogs and cats to reverse adverse opioid effects is 0.01 to 0.04 mg/kg. It may be given by the intravenous, intramuscular, subcutaneous, or endotracheal routes. Naloxone administration is generally safe in patients with opioid overdose, but very high dosage can initiate seizure activity. If there is no response initially, repeat doses should be administered and titrated to each patient's response.[3]

Naloxone may have a shorter duration of action than most opioids, and repeated doses or a continuous infusion may be necessary. A continuous infusion is administered by determining the amount of naloxone required to reverse respiratory depression, then administering two thirds of this dose every hour in a continuous infusion. Half of the loading dose should be administered 15 minutes after the initial dose because of a transient decline in the naloxone level 20 to 30 minutes after the initial bolus. The rate of the infusion should be titrated to maintain adequate ventilation.

Naloxone can be mixed in most intravenous fluids in varying concentrations.[35] The infusion is continued for the typical duration of effect of the involved opioid, then gradually reduced while the patient's respiratory and mental status are monitored closely. Continuous infusions have been used safely in both adults and children.[36,37] Larger-than-customary doses may be required to reverse the effects of codeine, methadone, propoxyphene, pentazocine, butorphanol, buprenorphine, and nalbuphine.[38]

83.6 PROGNOSIS

Asymptomatic patients overdosed with any of these drugs should be observed for a minimum of 24 hours. The prognosis for toxicity with most of these drugs is unknown, but as with other intoxication, the outcome depends on the quantity of drug ingested and the severity of clinical signs demonstrated on admission. Early decontamination and good supportive care can prevent serious CNS, respiratory, and cardiovascular depression.

83.7 SUGGESTED FURTHER READINGS*

DM Boothe: Control of pain in small animal: opioid agonists and antagonists and other locally and centrally acting analgesics. In DM Boothe (Ed.): *Small animal clinical pharmacology and therapeutics*. 2001, Saunders, St Louis, *A great review of the pharmacology of opioids in veterinary medicine*.

EA Martinez, KA Mealey: Muscle relaxants. In DM Boothe (Ed.): *Small animal clinical pharmacology and therapeutics*. ed 1, 2001, Saunders, St Louis, *A great review of the pharmacology of muscle relaxants in veterinary medicine*.

JC Murrell, LJ Hellebrekers: Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog. *Vet Anaesth Analg*. **32**, 2005, 117, *A great review of the clinical effects of* α_2*-agonists*.

* See the CD-ROM for a complete list of references

84 Chapter 84 Calcium Channel and β-Blocker Drug Overdose

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84.1 KEY POINTS

- Close regulation of intracellular calcium is essential for the body to accomplish many physiologic processes, including excitation-contraction coupling, impulse formation and conduction, and maintenance of vascular tone.
- Calcium channel blockers and β-blockers inhibit L-type voltage-sensitive calcium channels.
- The main physiologic derangements caused by overdose of these medications are negative inotropy and chronotropy, leading to decreased cardiac output, hypotension, tissue hypoperfusion, and shock.
- No single pharmacologic agent has been consistently effective for critically ill patients with these toxicities. A combination of antidotes may be required until the clinical signs have resolved.
- The prognosis depends on the quantity of drug ingested and the severity of signs. Early aggressive decontamination and good supportive care can prevent serious hemodynamic failure.

84.2 INTRODUCTION

Drugs classified as calcium channel and β-blockers frequently are prescribed for cardiovascular disease management. In humans, these drugs are effective in patients with hypertension, angina pectoris, cardiac arrhythmias, migraines, tremors, and bipolar disorder.[1] In veterinary medicine, calcium channel and β-blockers are used to treat cardiac arrhythmias, hypertrophic cardiomyopathy, and hypertension.[2-3]

Calcium plays a role in many physiologic processes, including impulse formation and conduction, excitation-contraction coupling, and maintenance of vascular tone. Close regulation of intracellular calcium is essential to accomplish these cardiovascular functions.[4] There are several types of calcium channels. Calcium channel blockers inhibit only the voltage-sensitive channels, which open in response to voltage changes across the membrane, for example during depolarization. There are three types of voltage-sensitive calcium channels, designated as neuronal (N-type), transient (T-type), and long lasting (L-type). The L-type channels are the most sensitive to the commercially available calcium channel blockers. β-Blockers inhibit the cardiac adrenergic system, modifying the L-type voltage-sensitive channels via a second messenger system.

L-type channels are located in various tissues but are found in highest concentration in the atria, vascular smooth muscle, and skeletal muscle. L-type voltage-sensitive calcium channels are activated as the transmembrane potential of the cell becomes progressively less negative during the upstroke of the action potential (phase 0). They have a prolonged opening time and high conductance, therefore allowing large amounts of calcium to pass rapidly into the cell.[5] Calcium channel and β-blockers interrupt calcium flux, leading to decreased intracellular calcium, depressing cardiovascular function.[5] Although calcium channel and β-blockers have different mechanisms of action, the physiologic effects, clinical signs, and treatment of toxicity are similar.[3]

84.3 METHOD OF ACTION

84.3.1 Calcium Channel Blockers

Calcium channel blockers exert most of their effects on cardiac myocytes, pacemaker cells, and vascular smooth muscle. They are classified into three major groups based on their structure, including the phenylalkylamines (e.g., verapamil), the benzothiazepines (e.g., diltiazem), and the dihydropyridines (e.g., amlodipine). Structural differences among the classes are associated with distinct binding sites on the calcium channel, resulting in differing potencies and tissue affinities (Table 84-1). Their structural heterogeneity leads to functional heterogeneity with regard to their vasodilator potency and their cardiac inotropic, chronotropic, and dromotropic effects.[1-3]

84.3.1.1 Cardiac Effects

The calcium ion is essential for impulse conductance through the cardiomyocytes. Pacemaker cells of the sinoatrial (SA) and atrioventricular (AV) nodes rely on the inward calcium flux through L-type and T-type channels to initiate a spontaneous diastolic depolarization (phase 4). Calcium channel blockers inhibit inward flow of calcium through the L-type channel, leading to slow SA activity, decreased conduction of impulses through the AV node, and therefore a decrease in heart rate and prolongation of the refractory period.[5] The negative chronotropic effect occurs primarily with the phenylalkylamines and benzothiazepines. With some calcium channel blockers, this effect may be attenuated or even abolished because of reflex stimulation of the sympathetic nervous system.[2]

Calcium plays an important role during excitation-contraction coupling in cardiac and vascular smooth muscles. Within Purkinje cells and myocytes, opening of the L-type calcium channels in response to membrane depolarization increases calcium conductance (phase 2 of the action potential). This inward flow of calcium triggers the release of additional calcium into the cytoplasm from the sarcoplasmic reticulum. 357 358 Intracellular calcium binds to troponin, changing its conformation and allowing interaction between actin and myosin so that contraction can occur. By decreasing the magnitude and rate of rise of the intracellular calcium concentration, the calcium channel blockers decrease calcium release from the sarcoplasmic reticulum, causing a decrease in the force of contraction.[2,5] This negative inotropic effect is seen most commonly with the phenylalkylamines and to a lesser extent with the benzothiazepines.[2] Most of the calcium channel blockers have a negative inotropic effect at high doses.[3]

Table 84-1 Expected Cardiovascular Effects of Calcium Channel Blocking Agents in Healthy Animals[2,3,34]

Generic Name	Trade Name	Chronotropic (HR)	Dromotropic (AV Conduction)	Inotropic (Strength)	Systemic Vascular Resistance	Coronary Resistance
Phenylalkylamines						
Verapamil	Calan, Verelan, Isoptin	0 or +	++	+	+	+
Benzothiazepines						
Diltiazem	Cardizem, Dilacor	0 or ++	++	0 or +	+	+
Dihydropyridines						
Nifedipine	Procardia, Adalat	0	0	0	++	++
Amlodipine	Norvasc	0	0	0	++	+

AV, Atrioventricular; *HR,* heart rate.

Key: *0,* no change; +, mild to moderate decrease; ++, moderate to marked decrease. This effect is rate dependent, being more pronounced at higher heart rates.

84.3.1.2

Vascular Effects

In vascular smooth muscle cells, opening of calcium channels increases the cytosolic calcium concentration. Calcium interacts with calmodulin, causing phosphorylation of the myosin light-chain and actin-myosin binding, resulting in smooth muscle contraction and vasoconstriction. Calcium channel blockers prevent the rise in intracellular calcium needed for formation of the calcium-calmodulin complex and thus cause dilation of systemic and coronary arteries and arterioles.[5] At therapeutic concentrations, they have minimal effect on the venous system. The phenylalkylamines affect both vascular and cardiac tissue, the benzothiazepines have intermediate selectivity, and the dihydropyridines exert a greater effect on vascular tissue.[2]

84.3.1.3

Pancreatic Effects

The β-cells on the pancreas also contain L-type calcium channels. Calcium influx into pancreatic islet cells via L-type channels is required for insulin release. High doses of calcium channel blockers may therefore cause serum glucose levels to rise while intracellular glucose stores fall. This is another mechanism by which calcium channel blocker overdose may impair cardiovascular function and lead to shock.[6-8]

84.3.2 β-Blockers

There are two types of β-receptors. β_1-Receptors are located primarily within the heart and adipose tissue. Stimulation results in increased heart rate, myocardial contractility, AV conduction velocity, and automaticity of subsidiary pacemakers. β_2-Receptors are found primarily in bronchial and smooth muscles, where they produce relaxation.[4] In human medicine, β-adrenergic blocking agents differ in their ability to block β-receptor types.[9] In veterinary medicine the primary drugs are propranolol (β_1-receptor and β_2-receptor blocker), atenolol (specific β_1-receptor blocker), esmolol (specific β_1-receptor blocker), and sotalol (β_1-receptor and β_2-receptor blocker).[3]

84.3.2.1 Cardiac Effects

Interactions between catecholamines and β-receptors in the cardiac cell membrane stimulate membrane-bound adenyl cyclase, which raises the intracellular concentration of cyclic adenosine monophosphate (cAMP). cAMP activates protein kinases that phosphorylate the L-type calcium channel, increasing myocellular calcium entry and the release of calcium from the sarcoplasmic reticulum. This calcium interacts with the myocardial contractile machinery, producing systole. Protein kinases phosphorylate a protein, phospholamban, that causes the sarcoplasmic reticulum to take up calcium more rapidly, enhancing relaxation (diastole).[5] In general, β-adrenergic blockade decreases transmembrane calcium flow by decreasing cAMP synthesis, thereby decreasing atrial and ventricular contractility and decreasing the heart rate by slowing the spread of excitation through the AV node.[3]

84.3.2.2 Pulmonary, Pancreatic, Gastrointestinal, Vascular, and Renal Effects

In the lung, stimulation of β_2-receptors promotes bronchodilation, and their blockade leads to bronchospasm. In the pancreas, β_2-receptors mediate insulin release, and their blockade leads to decrease in glycogenolysis, lipolysis, and gluconeogenesis. In the gastrointestinal (GI) tract and vascular smooth muscles, inhibition of β_2-receptors results in contraction. β_1-Receptors are also present in the kidney, where they mediate renin release.[4]

84.4 PHARMACOKINETICS

84.4.1 Calcium Channel Blockers

Calcium channel blockers are absorbed rapidly and almost completely from the GI tract but have extensive first-pass metabolism. Times to peak serum concentration are rapid: 20 to 45 minutes for immediate-release forms and 4 to 12 hours for sustained-release formulations and amlodipine besylate (which has a slower absorption rate) in dogs and cats.[2] The onset of action varies with the formulation. An animal that bites into and swallows a sustained-release product can show signs within 5 minutes, but one that swallows it whole may not show signs 358 for several hours and may have prolonged toxicity because of slower absorption.[10] Tissue distribution is 359 extensive in all classes. Calcium channel blockers are approximately 80% protein bound; therefore interaction with other protein-bound drugs may result in competition for binding sites. Additionally, animals with moderate to severe hypoproteinemia may develop higher blood concentrations.

Table 84-2 Therapeutic Dosage Ranges of Calcium Channel Blockers and β-Blockers Most Commonly Used in Dogs and Cats[2,3,12]

	Therapeutic Dosages	
Drugs	**Dogs**	**Cats**
Calcium Channel Blockers		
PHENYLALKYLAMINES		
Verapamil hydrochloride	0.1 to 5 mg/kg PO q8-12h 0.15 mg/kg IV over 2 minutes	—*
BENZOTHIAZEPINES		
Diltiazem hydrochloride	0.5 to 1.5 mg/kg PO q8h 0.25 mg/kg IV over 5 minutes	1.7 to 2.5 mg/kg PO q8h
DIHYDROPYRIDINES		
Amlodipine besylate	0.05 to 0.25 mg/kg PO q24h	0.625 mg/cat PO q24h
Nifedipine	0.5 mg/kg PO q8h	—
β-Blockers		
Propranolol	If severe cardiac disease: 0.1 to 0.5 mg/kg PO q8h If normal myocardial function: 2 mg/kg PO q8h	2.5 to 10 mg PO q8h
Atenolol	6.25 to 50 mg PO q12h	6.25 mg PO q12h
Esmolol	Loading dose: 0.25 to 0.5 mg/kg IV followed by constant rate infusion: 10 to 200 μg/kg/min IV	

IV, intravenous; *PO,* per os.

In humans, calcium channel blockers are metabolized in the liver by oxidative pathways, predominantly by cytochrome P450 CYP3A. Therefore their clearance will be decreased when hepatic function or blood flow is reduced.[1] The phenylalkylamines and benzothiazepines can interact with many drugs because they are strong inhibitors of hepatic microsomal enzymes. Similarly, their elimination can be slowed by drugs that inhibit hepatic enzymes (e.g., cimetidine), potentially increasing their cardiovascular effects and producing toxicity.[10,11] Elimination half-lives depend on the formulation (i.e., immediate versus sustained release) and in dogs and cats can vary from 2 to 30 hours. Excretion is primarily through urine and, to a lesser extent, bile and feces.[2]

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* Verapamil is not recommended for use in cats; the safety of this drug is questionable in this species.

84.4.2

β-Blockers

The pharmacokinetics of β-blockers, although well established in humans, remain unclear in small animals. The more lipid-soluble compounds (e.g., propranolol) require hepatic biotransformation before secretion and can therefore accumulate if there is decreased hepatic blood flow or hepatic insufficiency. They also have a large volume of distribution and enter the central nervous system (CNS) faster and more easily. In contrast, the water-soluble compounds (atenolol) are excreted by the kidney and can accumulate if there is renal insufficiency.

Esmolol is water soluble but does not accumulate in renal failure because it is metabolized by erythrocyte esterases.[12]

Channel selectivity and concurrent disease should be considered when prescribing these medications. For example, β_1-selective agents are safer than nonselective agents for diabetic patients or cats with asthma. In patients with heart failure that are subjected to chronic increases in circulating catecholamine concentrations and increased sympathetic nervous system activity, β-adrenergic receptors are down-regulated, and fewer receptors are available for β-blocker binding. However, many patients with compromised myocardial function rely on stimulated β-receptors to maintain a greater degree of myocardial contractility. Thus administration of even medium doses of a β-blocker can result in lethal decreases in contractility and heart rate.[3]

84.5 DIAGNOSIS OF OVERDOSE

Clinical signs associated with toxicity due to calcium channel or β-blockers generally reflect an extension of the therapeutic effects of the drugs (Table 84-2).[2,3,12] Distinctions among the various drug classes tend to disappear in overdose situations. The primary signs are negative inotropy and chronotropy leading to decreased cardiac output, hypotension, tissue hypoperfusion, and shock. In humans, most calcium channel and β-blocker overdoses are evident within 6 hours of ingestion, but clinical signs may be delayed when sustained-release preparations or sotalol are ingested.[9]

Although calcium channel and β-blocker overdoses often manifest similarly, subtle differences in the clinical picture may suggest poisoning with one class over another. Following calcium channel blocker toxicity, selectivity for cardiac versus vascular effects is decreased but not eliminated.[13,14] Vasodilation, particularly associated with agents that have more pronounced effects on vascular smooth muscle (e.g., dihydropyridines), results in hypotension, decreased systemic vascular resistance, and shock. Distinctions among the various β-blocker classes tend to disappear in overdose situations.[15]

The most common electrocardiographic findings following significant calcium channel blocker ingestion are sinus bradycardia, AV block, and junctional rhythms.[10,16] β-Blocker toxicity also causes bradycardia, but ventricular conduction defects tend to be more common in humans.[17] Mild hyperkalemia may be observed with toxic levels of β-blockers, and hypocalcemia is reported occasionally in calcium channel blocker poisoning.[9] Electrolyte disturbances may further lower the threshold for serious rhythm abnormalities.

Hyperglycemia is a common finding with calcium channel blocker toxicity because insulin release is inhibited.[6] Hypoglycemia rarely is encountered in β-blocker overdose in humans, despite decreased gluconeogenesis and glycogenolysis.[9]

Noncardiogenic pulmonary edema has been reported in association with calcium channel blockers and β-blockers.[10,18] This is thought to be secondary to either precapillary vasodilation resulting in increased transcapillary hydrostatic pressure,[19] or a secondary effect of massive sympathetic discharge.[20] Dyspnea caused by bronchospasm rarely is reported, although it can occur in an asthmatic that has ingested a β_2-receptor antagonist.

In humans, overdose of highly lipid-soluble β-blockers such as propranolol frequently manifests as CNS depression and seizures.[9] Seizures after ingestion of verapamil are rare but have been reported in animals[16] and humans.[11]

Terminal events in both calcium channel and β-blocker toxicity include worsening of shock with multiple organ failure (myocardial infarction, mesenteric ischemia, acute renal failure, coma) and, ultimately, cardiac arrest.

84.6 THERAPY

84.6.1 Asymptomatic Patients

84.6.1.1 Decontamination

GI decontamination should be performed in all asymptomatic animals that have accidentally ingested calcium channel or β-blockers (see Chapter 77, Approach to Poisoning and Drug Overdose). If the ingestion occurred within the previous 2 hours and the patient is stable, emesis is recommended. In cases of massive ingestion or in patients with an altered level of consciousness, gastric lavage should be performed. Activated charcoal with a cathartic should be given to absorb and hasten the excretion of any remaining toxicant. The patient should be stable before receiving activated charcoal, and care should be taken to protect the airway and closely monitor hemodynamics.[21] Two to four doses of activated charcoal should be administered if a sustained-release product was ingested.[10] For the following 24 hours, serial electrocardiograms, blood pressure measurements, and blood glucose concentrations should be monitored.

Elimination of calcium channel blockers and lipid-soluble β-blockers (e.g., propranolol) via extracorporeal removal procedures (e.g., hemodialysis, hemoperfusion) is ineffective because these compounds are highly protein bound and have large volumes of distribution. However, hemodialysis may remove water-soluble β-blockers (e.g., atenolol and esmolol).[9]

84.6.2 Symptomatic Patients

Controlling the clinical signs of symptomatic animals is the first priority, emphasizing establishment of an airway and providing adequate ventilatory and circulatory support. After venous access is obtained, hypotensive animals should receive intravenous fluids such as isotonic crystalloids or synthetic colloids for volume expansion (see Chapter 65, Shock Fluids and Fluid Challenge). Pharmacologic options for hypotensive patients include calcium, atropine, catecholamine pressors, glucagon, regular insulin and dextrose as needed, aminophylline, and digoxin.[7,8,11,22-32] All of these drugs have been tested in dogs with cardiogenic shock induced by calcium channel or β-blocker overdose.[7,8,23,28-32] No single agent has been consistently effective in critically ill patients with these toxicities; therefore a combination of drugs may be required. Affected patients should be treated and monitored continuously until clinical signs have resolved.

84.6.2.1 Calcium Salts

Intravenous administration of calcium is the initial treatment for calcium channel blocker and β-blocker overdose.[22] Calcium gluconate is readily available and easily administered through a peripheral or central catheter. Exogenous calcium administration increases the extracellular calcium concentration and thus its availability to the cell, thereby stimulating the sarcoplasmic reticulum to release more calcium into the cytoplasm, which is then available for diverse cellular functions. Calcium administration may improve cardiac conduction, inotropy, and blood pressure.[22,23]

The optimal dosage of calcium is unclear. In experimental dogs, increasing the serum calcium by 1 to 2 mEq/L resulted in a reversal of the negative inotropic effects of verapamil, and even greater increases in serum calcium resulted in improvement of depressed AV conduction and sinus node function.[22] Administration of a continuous calcium infusion titrated to a desirable heart rate and blood pressure has also been suggested.[9,24] Calcium gluconate (10%) can be given at a dosage of 0.5 to 1.5 ml/kg slowly intravenously. Excessively rapid injection can cause hypotension, cardiac arrhythmias, and cardiac arrest. Continuous infusions of calcium gluconate are administered at dosages of 10 to 15 mg/kg/hr IV. Calcium chloride can also be used, however care should be taken during its administration because this preparation is more irritating than the other parenteral calcium salts.[12] In general, an initial bolus dose of calcium is followed by a continuous infusion, with measurement of serum calcium at least twice daily. Serum calcium concentration should be maintained at normal levels, given the lack of evidence to support supraphysiologic calcium levels. Careful maintenance of patent intravenous access sites is very important to prevent injury secondary to extravasation of calcium solutions. Continuous electrocardiographic monitoring is recommended during administration. Although treatment with intravenous calcium salts is successful in many cases, other therapies should be added if the patient is refractory to calcium infusion. In patients with large overdoses, calcium alone may be ineffective because few if any channels are unblocked and calcium is unable to enter the cell to perform its functions.

84.6.2.2 Parasympatholytic and Sympathomimetic Agents

Atropine (0.02 to 0.04 mg/kg IV) is a vagolytic agent normally used to reverse bradycardia and AV blockade,[12] but it is inconsistently effective in the treatment of both calcium channel blocker and β-blocker intoxications.[11-13,25]

Adrenergic agents such as dopamine, dobutamine, norepinephrine, epinephrine, phenylephrine, and 360
isoproterenol may be required either alone or in combination to counter hypotension (see Chapter 176, 361
Vasoactive Catecholamines). These agents act by stimulating α-adrenergic and β-adrenergic receptors. Stimulation of β-adrenergic receptors causes the formation of adenyl cyclase and subsequently cAMP. Direct α-adrenergic receptor agonists promote calcium release from the sarcoplasmic reticulum through receptor-operated calcium channels, bypassing L-channel blockade.[5] The choice of agent depends on the hemodynamic picture of the patient and the responses to specific antidotes. β-Adrenergic receptor agonists such as dobutamine or isoproterenol would be logical choices when the toxicity primarily affects cardiac chronotropy and inotropy. Direct α-adrenergic receptor agonists may be a better choice if the toxicity is related primarily to decreased systemic vascular resistance. Combining α-adrenergic and β-adrenergic receptor agonists or using agents with both α-adrenergic and β-adrenergic effects may ameliorate both cardiac dysfunction and decreased systemic vascular resistance.

84.6.2.3 Glucagon

Glucagon is a polypeptide hormone[26] that binds to receptor sites that are distinct from L-type calcium channels and adrenergic receptors. It then stimulates adenyl cyclase, which results in the formation of cAMP, promoting calcium influx and stimulating the release of calcium from the sarcoplasmic reticulum. Glucagon's effects on adenyl cyclase also cause stimulation of the SA and AV nodes. As a result, glucagon has inotropic, chronotropic, and dromotropic properties.

Several animal model studies have evaluated the efficacy of glucagon for calcium channel and β-blocker overdoses, and they have shown that it increases heart rate and cardiac output and reverses second-degree and third-degree AV blocks. However, it does not have any effect on mean arterial blood pressure and does not appear to have any effect on survival rate. Glucagon is given as an intravenous bolus of 0.15 mg/kg followed by a constant infusion of 0.05 to 0.1 mg/kg/hr titrated to effect.[26]

84.6.2.4

Hyperinsulinemia and Euglycemia

In an unstressed state, myocytes oxidize free fatty acids for metabolic energy. However, in a state of shock, such as that associated with overdose of calcium channel blockers and β-blockers, myocytes use glucose for energy. Hypoinsulinemia prevents the uptake of glucose by myocytes, causing a loss of inotropy and shock. Calcium channel blockers inhibit insulin secretion, resulting in hyperglycemia and alterations in myocardial fatty acid oxidation.[8] Similarly, blockade of β_2-adrenergic receptors due to β-blocker toxicity impairs lipolysis, glycogenolysis, and insulin release.[27] Insulin may be effective because it increases lactate oxidation while switching myocardial cell metabolism from fatty acids to carbohydrates during shock, thus restoring calcium fluxes, resulting in a positive inotropic effect.[7,28,29] Therefore insulin therapy may improve contractility and increase peripheral vascular resistance by improving the uptake of carbohydrates and accelerating their oxidation by myocytes and smooth muscle cells.[29,33]

Lactic acidosis from toxicity-induced circulatory shock is partially a manifestation of poor tissue perfusion but is also due to mitochondrial dehydrogenase inhibition. In high concentrations, calcium channel blockers inhibit mitochondrial calcium entry into the sarcolemma and the mitochondrial membrane, which in turn can decrease pyruvate dehydrogenase activity. Pyruvate does not enter the Krebs cycle and lactate accumulates, producing metabolic acidosis. Insulin can increase myocardial pyruvate dehydrogenase activity, enhancing lactate oxidation and reversing the acidosis.[7]

Regular insulin is given as an intravenous bolus of 1 IU/kg, followed by an infusion of 1 IU/kg/hr for the first hour, followed by 0.5 IU/kg/hr with concurrent dextrose administration as needed until the toxicity resolves. Depending on the severity of the overdose, resistance to insulin-mediated glucose clearance may be significant.[27] Blood glucose should be monitored hourly or more frequently as needed, and dextrose supplemented as required to maintain euglycemia during the insulin infusion. Electrolyte abnormalities such as hypokalemia, hypophosphatemia, and hypomagnesemia may also occur, and their serum levels should be monitored every 12 to 24 hours and supplemented as required.

84.6.2.5

Others

The efficacy of many drugs for treating calcium channel blocker and β-blocker toxicity has been evaluated only in laboratory animal models and has not been validated in clinical trials. Nevertheless, some of these drugs are important to consider because they are readily available to most veterinarians. Aminophylline is a phosphodiesterase inhibitor that increases cAMP and therefore intracellular calcium translocation. It is capable of increasing heart rate and systemic arterial blood pressure in dogs with propranolol overdose.[30] Digoxin may increase the effectiveness of calcium salt treatment in patients with calcium channel blocker overdose;however, its safety remains unknown in this setting. By inhibiting the sodium-potassium-adenosine triphosphatase pump, digoxin increases intracellular sodium, which is then exchanged for calcium by a process that is not blocked by a calcium channel antagonist.[31,32]

84.6.2.6 Mechanical Support

Mechanical supportive measures may be necessary if pharmacologic therapy fails. Cardiac pacing, intraaortic balloon counterpulsation, and extracorporeal cardiopulmonary bypass have all been used in humans with calcium channel blocker overdose.[9] Although many veterinary centers are able to perform cardiac pacing, more advanced procedures typically are not available.

84.6.3 Supportive Care

Supportive care consists of airway protection and management, adequate ventilation, and hemodynamic monitoring. Endotracheal intubation may prevent pulmonary aspiration during vomiting or gastric instillation of charcoal, and may improve cardiac output and survival. A central venous catheter can provide a portal for pulmonary artery catheterization, for monitoring central venous pressure, to adjust fluid and to administer calcium salts (which are irritating to peripheral veins). A urinary catheter should be inserted to monitor urine production, and nutrition should be addressed as soon as possible.

84.7 CONCLUSION

Flow of calcium across cell membranes is necessary for cardiac automaticity, conduction, and contraction, as well as maintenance of vascular tone and insulin secretion. Calcium channel blockers and β-blockers impede calcium 361
flux across cell membranes, thereby depressing myocardial contractility, slowing sinus and AV nodal conduction, 362
and causing vasodilation. The prognosis depends on the quantity of drug ingested and the severity of signs at initial evaluation. Early decontamination and good supportive care can prevent serious hemodynamic failure.

84.8 SUGGESTED FURTHER READING*

KL Cooke, PS Snyder: Calcium channel blockers in veterinary medicine. *J Vet Intern Med*. **13**, 1995, 444, *An excellent review of the pharmacology of calcium channel blockers and their therapeutic uses in veterinary medicine*.

T Holder: Calcium channel blocker toxicosis. *Vet Med*. **95**, 2000, 912, *Review of calcium channel blocker toxicosis in veterinary medicine using the American Society for the Prevention of Cruelty to Animals National Animal Poison Control database*.

PD Pion, WA Brown: Calcium blocking agents. *Compend Cont Educ*. **17**, 1995, 691, *An excellent review of the pharmacology of calcium channel blockers and their therapeutic uses in veterinary medicine*.

* See the CD-ROM for a complete list of references

85

Chapter 85 Digoxin Overdose

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85.1

KEY POINTS

- Cardiac glycoside toxicity is not uncommon because of the narrow therapeutic index, variability in patient sensitivities to the medications, and alterations in pharmacodynamics due to comorbid disease.
- Cardiac glycosides cause positive inotropy through inhibition of membrane-bound sodium and potassium-activated adenosine triphosphatase (Na^+,K^+-ATPase).
- Noncardiac manifestations of digoxin overdose include gastrointestinal disturbances and neurologic abnormalities.
- Cardiac manifestations of digoxin overdose are extremely variable but classically include arrhythmias characterized by increased automaticity with or without conduction delays.
- Patients with alterations in serum electrolytes, renal disease, endocrine disease, increased sympathetic nervous system activity, or concurrent drug administration may be more susceptible to digoxin toxicosis.
- Treatment of digoxin toxicosis involves gastrointestinal decontamination, recognition and treatment of life-threatening arrhythmias, normalization of serum electrolyte concentrations and, in severe cases, administration of Fab fragments of digoxin-specific antibodies.

85.2

INTRODUCTION

Cardiac glycosides, the most common of which is digoxin, have an extremely narrow therapeutic index. In addition, there is marked variability in the sensitivity of individual patients to the toxic effects of cardiac glycosides. Therefore, it is not uncommon for both human and veterinary patients to exhibit clinical evidence of toxicity. Although information on the incidence of toxicosis in veterinary patients is not available, it has been reported in up to 35% of digitalized human patients.[1]

Several mechanisms may contribute to toxicosis. Digoxin is excreted primarily by the kidneys. Renal insufficiency may therefore increase serum concentrations. Congestive heart failure, renal disease, and hepatic disease may alter the metabolism or volume of distribution of digoxin, as can other medications used for cardiac or other concurrent diseases.[2] Serum electrolyte abnormalities, particularly alterations in potassium, calcium, and magnesium, can potentiate cardiac glycoside toxicity.[2] Although there is a clinical assay for serum digoxin concentrations, toxicity is still common because serum concentrations do not correlate directly with clinical evidence of toxicity.

The most important aspect of digoxin toxicosis management is early recognition. Some patients with signs of mild toxicosis may respond to withdrawal of the medication. Therapy of the patient suffering from severe toxicosis includes, but is not limited to, gastrointestinal decontamination, fluid therapy, correction of serum electrolyte and acid-base abnormalities, treatment of congestive heart failure, antiarrhythmic or pacemaker therapy, and in severely affected animals, the administration of Fab fragments of digoxin-specific antibodies. The incidence and severity of digoxin toxicity has declined since the development of alternative drugs for treating supraventricular arrhythmias, the widespread availability of assays for serum digoxin levels, the identification of interactions between digoxin and other medications, and the increased vigilance of clinicians.[1] Although the human literature still suggests a role for digoxin for patients with congestive heart failure,[3] it is likely that digoxin use will wane as newer and safer drugs become available.

85.3 MECHANISM OF ACTION

An understanding of digoxin's mechanism of action is essential to comprehend the toxicologic features of this medication. The beneficial effects of the cardiac glycosides in animals with congestive heart failure can be attributed primarily to their positive inotropic and negative chronotropic effects. Their positive inotropic effect is caused by the inhibition of the membrane-bound Na^+,K^+-ATPase on the myocardial cell membranes. Digoxin competitively binds to the site that potassium typically occupies and therefore stops activity of approximately 30% of these pumps when given at therapeutic levels. As the activity of this enzyme is impaired, there is an accumulation of intracellular sodium and an increase in intracellular osmolality. The cell attempts to counter these changes by increasing the efflux of sodium and influx of calcium through the sodium-calcium cation exchanger. The increased intracellular sodium concentration also reduces the transmembrane gradient that drives calcium outside of the cell during repolarization, decreasing calcium efflux. The subsequent increase in intracellular calcium further triggers the release of stored intracellular calcium from the sarcoplasmic reticulum during systole, thus increas-ing the amount of cytosolic calcium available to interact with the contractile proteins. This ultimately results in an increase in myocardial contractility.[4]

Cardiac glycosides exhibit both direct and neurally mediated actions on the atrial and ventricular myocytes, as well as on the specialized conduction tissues within the myocardium. At therapeutic serum levels, digoxin indirectly depresses the rate of sinoatrial node depolarization by increasing vagal tone. In addition, the drug decreases atrial fiber automaticity and increases maximal diastolic resting potential in both atrial and atrioventricular (AV) nodal tissues.[4,5] These effects are due, at least in part, to an increase in vagal tone as well because they are blocked by atropine administration.[6] In addition, at therapeutic levels digitalis causes a predominantly vagally mediated prolongation of the effective refractory period in these tissues, which results in decreased conduction velocity in AV nodal tissue. This action accounts for the utility of digitalis in terminating reentrant arrhythmias involving the AV node, and in controlling the ventricular response rate to atrial fibrillation.[4] At higher concentrations, however, digoxin may increase resting membrane potential, increase automaticity, and increase sympathetic nervous system activity.[6] These effects, in conjunction with increases in intracellular calcium and altered impulse conduction velocities, may result in severe and life-threatening arrhythmias.

The cardiac glycosides have an important role in the modulation of abnormal autonomic tone that is classically seen in moderate to severe heart failure. Patients in congestive heart failure develop increased sympathetic tone in response to alterations in cardiac output. Mitigation of this excessive sympathetic tone is thought to contribute to the efficacy of digoxin for the treatment of heart failure. In patients with moderate to severe heart failure, infusion of a cardiac glycoside increases forearm blood flow and cardiac index and decreases heart rate and skeletal muscle sympathetic activity (a surrogate of the central sympathetic nervous system tone).[7] In addition, digoxin inhibits the sodium pump in neuronal cells (i.e., baroreceptor cells), resulting in stimulation of parasympathetic and inhibition of sympathetic nerves.[8] As a result, the cardiac glycosides alter carotid baroreceptor reflex responsiveness to changes in carotid sinus pressure in animals with heart failure.[10] Because cholinergic innervation is more prominent in the atrial and AV nodal tissues, the cholinomimetic actions of digoxin affect these tissues to a greater extent than the Purkinje fibers or the ventricular myocardium.[4] On the basis of these observations, among others, modulation of neurohormonal activation could be an important mechanism contributing to the efficacy of digoxin in the treatment of heart failure.

85.4 NONCARDIAC MANIFESTATIONS OF TOXICOSIS

Noncardiac manifestations of digoxin toxicosis are relatively nonspecific and develop as a result of inhibition of Na^+,K^+-ATPase in other excitable tissues, such as smooth muscle cells and the central nervous system. Animals with extracardiac toxicosis most commonly have signs referable to the GI system, including anorexia, nausea, vomiting, or diarrhea. These may be the result of direct effects of cardiac glycosides on the GI tract; however, vomiting may also result from central stimulation of the chemoreceptor trigger zone.[1] Neurologic effects may manifest as depression, fatigue, restlessness, disorientation and, uncommonly, seizures. Visual deficits and convulsions have been documented rarely in human patients.[1] Thrombocytopenia and alterations in follicle-stimulating hormone, leuteinizing hormone, and sex hormone levels have been seen infrequently in human medicine.[11]

85.5 CARDIAC MANIFESTATIONS OF TOXICOSIS

Cardiac manifestations of digoxin toxicosis are common and should be of paramount importance to the critical care clinician. Digitalis uptake by diseased myocardium differs from that of normal myocardium; therefore arrhythmias may occur at therapeutic serum levels.[12] Although extracardiac toxicity occurs frequently, studies evaluating the side effects of digoxin in Beagle dogs suggest that electrocardiographic (ECG) abnormalities are commonly underdiagnosed, frequently, although they are often the first sign of toxicity in dogs.[13] Therefore ECG monitoring is recommended for all patients receiving digoxin that have clinical signs suggestive of toxicosis. There are no arrhythmias pathognomonic for digitalis toxicosis; however, toxicity should be strongly suspected in patients that have evidence of increased automaticity with or without concomitant conduction delays.[1] More common arrhythmias include sinus bradycardia, paroxysmal atrial tachycardia, varying degrees of AV block, ventricular premature beats, and ventricular tachycardia (see Chapters 45, 46, and 47, Bradyarrhythmias and Conduction Abnormalities, Supraventricular Tachyarrhythmias, and Ventricular Tachyarrhythmias, respectively).[6] However, even if these arrhythmias are present, toxicity may be confirmed only by resolution of the arrhythmia following withdrawal of the drug or shortly following the administration of Fab fragments of digoxin-specific antibodies.

As discussed previously, digoxin has variable effects on the electrical tissues of the heart. In patients that are in sinus rhythm, digoxin acts to slow the heart rate by increasing vagal tone and improving cardiac performance. However, at toxic serum levels digoxin directly suppresses activity in the sinoatrial node, which may result in severe sinus bradycardia, sinus arrest, or sinus exit block.[1]

At therapeutic levels, cardiac glycosides have minimal effects on atrial tissues; however, at toxic levels digoxin may increase the resting membrane potential, shorten action potential duration,[8] and increase automaticity in atrial tissues, resulting in a variety of supraventricular arrhythmias. Paroxysmal atrial tachycardia resulting from increased atrial automaticity is common in animals with digoxin toxicosis and was previously thought to be pathognomonic for this condition. AV junctional tachycardia is also a relatively common arrhythmia associated with digoxin toxicosis and results from enhanced automaticity of junctional pacemakers with or without suppression of pacemakers in the sinoatrial node. At therapeutic levels, digoxin acts to prolong AV nodal refractoriness largely through increases in parasympathetic tone. However, at toxic levels, cardiac glycosides act directly to prolong the AV nodal refractory period.[14] Conduction block commonly results and may include any degree of AV block, including complete heart block. Mobitz type II second-degree AV block resulting from digoxin toxicosis is rare.[1]

Ventricular arrhythmias resulting from digoxin toxicity are far less common than supraventricular arrhythmias. When seen, ventricular arrhythmias are the result of enhanced automaticity and triggered activity. The most common manifestation of digitalis toxicosis in ventricular tissues is frequent ventricular premature beats; however, other ventricular arrhythmias may include ventricular tachycardia, ventricular bigeminy, or ventricular trigeminy.[14] Ventricular fibrillation may occur but is often a late manifestation of toxicosis. Triggered activity differs from abnormal automaticity in that triggered activity is linked to, and triggered by, a previous action potential. There are two types of triggered activity: early after-depolarizations and delayed after-depolarizations. Delayed after-depolarizations occur when the repolarized resting membrane oscillates to threshold potential and depolarizes in the late phases of the action potential. This activity is thought to be elicited by alterations in intracellular calcium levels, classically seen in patients treated with cardiac glycosides.[15] However, other serum electrolyte abnormalities such as hypokalemia, which may be present in patients with congestive heart failure, may enhance fluctuations in membrane potential. Early after-depolarizations are rarely seen as a result of digoxin toxicosis.

Although modulation of abnormal autonomic tone in congestive heart failure is one of the beneficial effects of therapeutic levels of digoxin, toxic levels of the drug directly increase sympathetic nervous system activity.[8] Increased sympathetic nervous system activity in conjunction with increased automaticity and conduction delays predispose the myocardium to the genesis of severe and life-threatening atrial and ventricular arrhythmias.

summary, the presence of arrhythmias in any patient receiving digoxin should prompt suspicion of and evaluation for toxicity. The recommended therapeutic serum level of digoxin is 0.8 to 2.5 ng/ml in both the dog and the cat.[4,9] The risk of toxicity has been shown to increase if concentrations exceed 2.0 to 2.5 ng/ml in the dog.[8] Steady-state serum levels of 2.4 to 2.9 ng/ml have been correlated with signs of mild toxicity in the cat.[9] Cats are thought to be more susceptible to the toxic effects of digoxin than dogs. Because of the poor correlation between serum levels and clinical evidence of toxicity, however, toxicity should be confirmed only by resolution of clinical signs following withdrawal of the drug or shortly following the administration of Fab fragments of digoxin-specific antibodies (see Treatment section below).

85.6 FACTORS CONTRIBUTING TO INCREASED RISK OF TOXICOSIS

Concurrent diseases may predispose to glycoside toxicity by causing alterations in drug metabolism, excretion, or volume of distribution (Box 85-1). Patients with alterations in renal function are predisposed to toxicosis because digoxin under-goes predominantly renal excretion. In addition, advanced renal disease may alter the volume of distribution of digoxin.[2] Patients with thyroid-related disease are prone to toxicity; hypothyroid patients classically have delayed digoxin clearance, and hyperthyroidism causes a decrease in serum digoxin levels. Alterations in digoxin distribution and clearance are thought to be due to altered density of Na^+,K^+-ATPase in various body tissues as a direct response to thyroid hormone.[11]

Activation of the sympathetic nervous system occurs in various disease states in an effort to maintain cardiac output and blood pressure. Catecholamines, both endogenous and exogenously administered, may potentiate arrhythmia formation by increasing the heart rate and force of contraction which subsequently increases myocardial oxygen demand. Stimulation of α-receptors causes coronary vasoconstriction, which may lead to diminished coronary blood flow and ischemia. However, catecholamines may also directly enhance arrhythmogenicity by enhancing the cellular influx of sodium and calcium, leading to enhanced automaticity, triggered activity, and reentrant arrhythmias.[15] Acidosis may potentiate arrhythmias by shortening the action potential duration and altering the resting membrane potential.[16] Hypoxemia frequently results in arrhythmias similar to those seen with digitalis excess, and humans with pulmonary disease may exhibit increased sensitivity to digoxin.[1] Although advanced age may be a risk factor for digoxin toxicity in humans, it is difficult to distinguish whether it is an independent risk factor because elderly patients have a higher prevalence of concurrent disease.[1]

Changes in serum electrolyte concentrations, particularly potassium, calcium, and magnesium, predispose patients to digoxin toxicosis. Cardiac glycosides bind preferentially to Na^+,K^+-ATPase following their phosphorylation; extracellular potassium promotes dephosphorylation at this site and causes a decrease in cardiac glycoside binding affinity for the enzyme. Conversely, low serum potassium concentrations increase the risk of toxicity by facilitating the attachment of glycosides to Na^+,K^+-ATPase. In addition, serum potassium independently affects resting membrane potential, leading to altered automaticity and AV nodal conduction. Hypokalemia both increases myocardial uptake[1] and decreases renal excretion of digoxin.[16] Hypercalcemia potentiates digitalis-induced arrhythmias by increasing ventricular automaticity and worsening the intracellular calcium overload that is already present with digoxin toxicity. Like potassium, serum calcium levels may independently affect resting membrane potential, leading to altered impulse generation and conduction.[14] Hypomagnesemia is common in patients receiving long-term diuretic therapy for heart failure and may increase the risk of digitalis-induced arrhythmias. However, this association has yet to be confirmed because there is a poor correlation between serum and tissue concentrations of magnesium.[1] Concurrent administration of additional drugs may also predispose patients to digoxin toxicity by altering the pharmacokinetics or pharmacodynamics of the parent compound. Several drugs have been implicated, including commonly used diuretics, quinidine, verapamil, cimetidine, various antimicrobials, and glucocorticoids.[4]

85.6.1

Box 85-1 Factors That May Increase Susceptibility to Digoxin Toxicity

- Electrolyte disturbances (especially potassium, calcium, and magnesium)
- Renal disease
- Thyroid disease
- Increased sympathetic tone
- Acidemia
- Concurrent drug administration (i.e., diuretics, glucocorticoids, antibiotics)

85.7

TREATMENT

Effective treatment of digoxin toxicosis is dependent on early recognition and intervention. Less severe forms of toxicosis, such as GI disturbance or mild arrhythmias that do not compromise hemodynamic stability, may be treated by withdrawing the medication and monitoring the patient's clinical signs and ECG until signs resolve. However, human guidelines recommend that patients with evidence of clinical deterioration or hemodynamic instability receive prompt and aggressive therapy.[11]

First-degree and second-degree AV block and sinus bradycardia often are responsive to atropine. Temporary pacemaker treatment is indicated for severe bradycardia or heart block that is unresponsive to atropine.[5] Several antiarrhythmic medications have been used to treat digitalis-induced ventricular arrhythmias. Lidocaine and phenytoin are among the most useful of these medications because they effectively terminate arrhythmias by suppressing ventricular automaticity, while exhibiting minimal effects on the sinus node, or on sinoatrial, AV nodal, or His-Purkinje conduction.[1] Quinidine and procainamide should be avoided for the treatment of ventricular arrhythmias arising from suspected digitalis toxicity because these agents may further suppress AV nodal and sinoatrial conduction. β-Blockade may be useful for treating ventricular arrhythmias induced by digoxin; however, these agents may also decrease contractility and worsen conduction block.[17] Esmolol, a β-adrenergic antagonist, may be especially useful in patients in with questionable contractility because it is an ultra short-acting drug. However, caution must still be exercised.

Alterations in serum electrolyte levels, notably potassium and calcium, may significantly enhance the arrhythmogenic effects of digoxin.[4] Administration of potassium salts has therefore been advocated for animals with decreased or normal serum potassium concentrations to decrease binding affinity of glycosides for the Na^+,K^+-ATPase.[17,18] A massive digoxin overdose may result in hyperkalemia that should be treated promptly (i.e., insulin and dextrose administration) because high serum potassium levels may lead to asystole (see Chapter 55, Potassium Disorders). GI decontamination with activated charcoal is indicated in patients with a history of recent ingestion, and other binding agents such as colestipol and cholestyramine are also effective[17] (see Chapter 77, Approach to Poisoning and Drug Overdose). Hemodialysis is not indicated for digoxin toxicosis because of the drug's large volume of distribution.[4] Hemodialysis for patients with digoxin overdose is limited to those with severe, life-threatening hyperkalemia.

The development of digoxin-specific Fab fragments has greatly enhanced treatment success in patients with life-threatening toxicity. Following administration, digoxin-immune Fab fragments bind to and inactivate circulating unbound drug by inhibiting binding to the Na^+,K^+-ATPase on the cell membrane.[18] The glycoside-antibody complex is subsequently eliminated in the urine. Total serum concentrations of digoxin will markedly rise after administration of Fab fragments; however, these represent a nonpharmacologically active form of the drug.[19] Digoxin-immune Fab (Digibind) has been used effectively to treat digoxin overdose in dogs with minimal side effects, although the cost may be prohibitive for some clients.[19,20] The dosage administered is calculated by first determining the total body load of digoxin:

$$\text{Serum digoxin concentration}\,(\text{ng}\,/\,\text{ml}) \times 14\,\text{L}\,/\,\text{kg} \times \text{body weight}\,(\text{kg})\,/\,1000$$

The number of vials administered is adjusted to account for the volume of distribution in dogs as follows:

$$\text{Number of vials} = \text{body load of digoxin}\,(\text{mg}) \div 0.6\text{mg of digoxin}$$ [20]

Complications following treatment typically are related to rapid reversal of the pharmacologic effects of digoxin; therefore intensive monitoring is essential after administration.

85.8 CONCLUSIONS AND PROGNOSIS

Digoxin toxicity is often manifested by several clinical signs, most importantly cardiac arrhythmias. Even with the ability to measure serum digoxin levels, it may prove difficult to differentiate between arrhythmias secondary to the drug versus those resulting from intrinsic heart disease. However, treatment of the arrhythmias is often primarily accomplished by withdrawal of the drug, although more sophisticated treatment strategies do exist, as explained earlier. Hemodialysis is not useful because most of the drug has a large volume of distribution and is tissue bound.

The most important aid in the treatment of digoxin toxicity is prevention, especially because there is a narrow window of therapeutic safety. Most animals can be successfully treated by withdrawal of the drug and antiarrhythmic therapy, although life-saving treatment with digoxin-specific Fab fragments may be necessary and are often cost prohibitive in larger animals.

85.9 SUGGESTED FURTHER READING*

DM Boothe: Therapy of cardiovascular diseases. In DM Boothe (Ed.): *Small animal clinical pharmacology and therapeutics*. 2001, Saunders, Philadelphia, *A comprehensive reference book that reviews the mechanism of action, pharmacologic effect, clinical uses, pharmacokinetics and pharmacodynamics, and toxicities associated with drugs used in veterinary practice*.

RL Hamlin: Clinical toxicology of cardiovascular drugs. *Vet Clin North Am Small Anim Pract*. **20**, 1990, 469, *A review article discussing mechanisms by which underlying cardiac disease alters pharmacokinetics and pharmacodynamics of cardiac drugs. Includes brief, salient reviews of commonly encountered cardiovascular drug toxicities in small animal practice*.

MD Kittleson: Diagnosis and treatment of arrhythmias. In MD Kittleson, RD Kienle (Eds.): *Small animal cardiovascular medicine*. 1999, Mosby, St Louis, *An excellent small animal cardiovascular medicine reference textbook. Includes basic cardiovascular physiology and pathophysiology, common small animal cardiovascular diseases, and therapeutic recommendations*.

* See the CD-ROM for a complete list of references

86 Chapter 86 Cyanide

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86.1 KEY POINTS

- Sources of cyanide poisoning include environmental contamination, smoke inhalation, food sources, and sodium nitroprusside therapy.
- There are no known reports in the veterinary literature of cyanide toxicity from naturally occurring sources in companion animals. However, cyanide poisoning should be suspected in smoke inhalation victims or animals on prolonged infusions of sodium nitroprusside.
- Histotoxic hypoxia is the hallmark of cyanide poisoning, resulting from inhibition of aerobic metabolism.
- Diagnosis of cyanide toxicity typically is based on history, physical examination, and presence of a lactic acidosis. However, whole blood cyanide concentration is considered to be the gold standard for diagnosis.
- Antidotes for cyanide toxicity include intravenous sodium nitrite and sodium thiosulfate. Hydroxycobalamin may also be considered as an adjunctive therapy.
- Any patient receiving sodium nitroprusside therapy who exhibits central nervous system signs, cardiovascular instability, and an increasing metabolic acidosis should be assessed for cyanide toxicity. Sodium nitroprusside therapy should be discontinued immediately and an antidote administered.

86.2 INTRODUCTION

Cyanide is readily available and accessible in a variety of forms. Historically, cyanide was used in warfare in the volatile, water-soluble, liquid forms of cyanide and cyanogen chloride.[1] Cyanide salts, which produce a cyanide gas when mixed with acid, are used in industrial applications including chemical synthesis, electroplating, tanning, metallurgy, printing, agriculture, photography, manufacturing of paper and plastics, and as fumigants and insecticides. Industrial solvents, as well as artificial nail and glue removers, contain the nitriles, acetonitrile and propionitrile.[1] These substances do not contain cyanide, but they are metabolized to cyanide in the liver.[1]

Cyanide is also found in very low concentrations in foods in the form of amygdalin, a sugar compound with cyanide attached. Once ingested, amygdalin is metabolized to hydrogen cyanide in the gastrointestinal tract. The most well-known source of cyanide in food is the seeds and fruit pits from the *Prunus* spp (apples, chokecherries, bitter almonds, and apricots). Other food sources known to contain cyanide include lima beans and cassava.[1]

Another possible source of cyanide exposure is enclosed space fires. Combustion of many substances such as nylon, plastics, wool, and silk may release hydrogen cyanide gas.[1] Therefore victims of smoke inhalation are at risk for cyanide poisoning in addition to carbon monoxide poisoning[2] (see Chapters 28 and 87, Smoke Inhalation and Carbon Monoxide, respectively).

Finally, cyanide exposure can result from iatrogenic sources. The antihypertensive agent, sodium nitroprusside, can release up to five cyanide groups during its metabolism, and toxicity may develop as cyanide accumulates.[1,3]

Despite widespread cyanide sources and cyanogenic compound use, there are no known reports of cyanide toxicity from naturally occurring sources in companion animals. However, cyanide toxicity may have contributed to reportedly abnormal mucous membrane color in dogs following smoke inhalation, and to a loss of consciousness and abnormal cardiovascular variables in cats following smoke inhalation.[4,5]

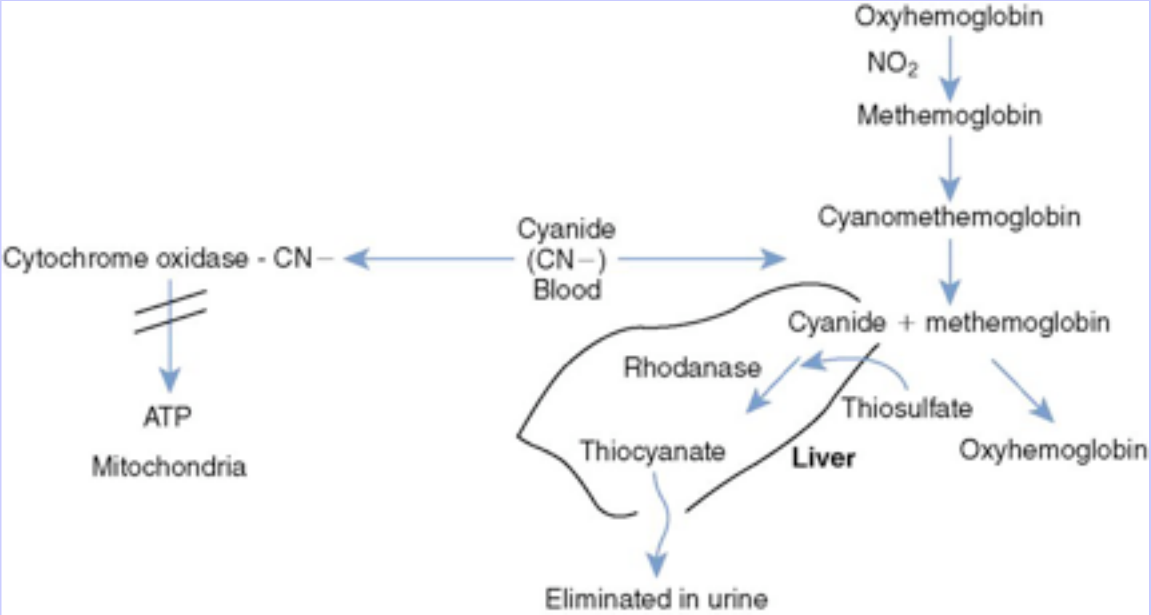
The hallmark of cyanide poisoning is histotoxic hypoxia due to inhibition of aerobic metabolism.[1] This can lead to the “brick-red” mucous membrane color indicative of poor tissue oxygen extraction that has been classically associated with cyanide toxicity. Because of the disruption of cellular respiration, a switch to anaerobic metabolism occurs and results in a significant metabolic acidosis with dramatically elevated lactate concentrations.[1] Death from cyanide poisoning can happen quickly; however, antidotes are available and typically are effective if administered in time.

86.3 MECHANISMS OF TOXICITY

Cyanide is well known for its high degree of lethality and has been studied extensively in animal models. In a dog model of cyanide poisoning, the lethal dose, or LD_{50}, of potassium cyanide was found to be 2.4 ± 0.2 mg/kg[6] and the lethal blood level of cyanide was found to be 438 ± 40 μg/dl.[6] This potency is a result of cyanide's rapid diffusion into tissues and binding to target sites. Intravenous and inhalation exposures to cyanide produce the most rapid onset of signs, within seconds to minutes, and toxicity from ingestion of cyanide or cyanogenic compounds can occur within minutes to hours.[1]

Cyanides are present in low concentrations in the environment; therefore several intrinsic biochemical pathways for cyanide detoxification exist. The most important route for cyanide excretion is through the formation of thiocyanate, which is subsequently excreted in the urine through the kidneys.[1] Thiocyanate is formed primarily in the liver, directly through the activity of the rhodanase enzyme and indirectly via the enzymes 3-mercaptopyruvate sulfurtransferase and thiosulfate reductase.[1,3] These enzymes are responsible for combining cyanide and sulfur to form thiocyanate. Despite these intrinsic mechanisms for cyanide detoxification, these enzyme systems are easily overwhelmed during cyanide poisonings because of the body's limited supply of sulfur (Figure 86-1).[1]

Figure 86-1 Cyanide binds to cytochrome oxidase in the mitochondria, resulting in inhibition of the electron transport chain and loss of aerobic metabolism and generation of adenosine triphosphate. Nitrites react with oxyhemoglobin to form methemoglobin, which draws cyanide out of the mitochondria and forms cyanomethemoglobin. The enzyme rhodanase combines thiosulfate with cyanomethemoglobin to form thiocyanate, which is excreted by the kidneys and eliminated in the urine. Methemoglobin is converted back to oxyhemoglobin by the enzyme methemoglobin reductase.



The hallmark of cyanide poisoning is histotoxic hypoxia through inhibition of the terminal enzyme in oxidative phosphorylation. Cyanide has a high binding affinity for the ferric iron on the cytochrome a_3 portion of mitochondrial cytochrome oxidase. The binding of cyanide to cytochrome oxidase results in inhibition of oxidative phosphorylation.[7,8] Although the mitochondria remain exposed to an adequate oxygen supply, there is impaired oxygen extraction and use. The result is a shift to anaerobic metabolism, a substantial decrease in adenosine triphosphate synthesis, and depletion of cellular energy stores.[7,8] This switch to anaerobic metabolism for cellular energy production leads to an accumulation of lactic acid and resulting metabolic acidosis (see Figure 86-1).[7,8] Some cyanide will also bind to the ferrous (Fe^{2+}) iron of normal hemoglobin. Cyanohemoglobin is unable to transport oxygen, further contributing to tissue hypoxia.[7]

As cyanide accumulates, the brain and the heart are severely and rapidly affected. Central inhibition of respiratory centers leads to hypoventilation, and myocardial depression results in decreased cardiac output. These derangements further contribute to tissue hypoxia.[8]

86.4 CLINICAL MANIFESTATIONS

Exposure to high concentrations of cyanide can result in death within seconds to minutes. In cases of more prolonged onset of toxicity, the clinical signs reflect a progressive intracellular hypoxia. In a study of Beagle dogs that received sublethal doses of cyanide, the first clinical signs seen were dyspnea and tachycardia.[9] The lack of oxygen extraction in the tissues may cause cherry red mucous membranes and flushed skin. As cellular hypoxia worsens, a loss of consciousness occurs, progressing to coma with fixed dilated pupils, hemodynamic compromise, arrhythmias, generalized seizures, apnea, cardiac arrest, and death.[1] Neurogenic pulmonary edema may also occur.[8] Cyanosis is typically a late sign that is noted at the moribund stage of apnea and circulatory collapse.[8]

86.5 DIAGNOSIS

Blood cyanide concentration is the gold standard for confirming acute cyanide poisoning. However, emergency measurement of blood cyanide concentrations is rarely available, nor is there time for laboratory confirmation in a patient with suspected cyanide poisoning before initiating treatment.[7,2]

Initial physical examination and history findings, such as being in a fire or ingestion of amygdalin-containing foods such as apricot pits, may suggest cyanide toxicity. The absence of cyanosis in a spontaneously breathing patient that has signs compatible with severe hypoxia should suggest the diagnosis.[8] The smell of bitter almonds may be appreciated, but only about 40% to 60% of the human population possess the gene necessary to detect this odor.[7,8]

The characteristic laboratory finding in patients with cyanide toxicity is a metabolic acidosis with an elevated lactate concentration. Lactic acidosis will also be reflected by an elevated anion gap.[7,8] Cyanide-induced cardiovascular failure may further elevate the lactate concentration.[7] In humans with cyanide poisoning, lactate concentrations greater than 8 mmol/L may be suggestive of a blood cyanide concentration of at least 1 mg/dl.[2]

Because cyanide inhibits the extraction of oxygen from the blood, more oxygen than normal may be present in the venous circulation. This may be reflected by an increase in the venous partial pressure of oxygen (>40 mm Hg), an increased measured peripheral venous oxygen saturation (>70%), or a narrowing of the normal difference between the measured arterial oxygen saturation and the measured central venous or pulmonary artery oxygen saturation.[7,8] In other words, the arterial and central venous oxygen saturation will approach each other, and the central venous oxygen saturation will be greater than 70%.[7] These findings, along with compatible clinical signs and historical findings, may suggest cyanide poisoning.

Finally, because cyanide binds to the ferrous iron of hemoglobin-forming cyanohemoglobin, the arterial saturation (measured with a co-oximeter) will be decreased.[7] However, pulse oximetry readings will be unaffected.

86.6 TREATMENT

Cyanide is extremely quick acting, so there is often limited time available for treatment. For patients presenting within 1 hour of ingestion and without clinical signs, gastric lavage should be performed followed by administration of activated charcoal (see Chapter 77, Approach to Poisoning and Drug Overdose). One gram of activated charcoal binds only 35 mg of cyanide. Despite this low level of binding, activated charcoal administration (1 g/kg) may be helpful because the lethal dose of cyanide is relatively small.[8]

Supplemental therapy with 100% oxygen is recommended. It is theorized that oxygen therapy increases the rate of displacement of cyanide from cytochrome oxidase, enabling the electron transport system to resume function.[10] However, hyperbaric oxygen therapy remains controversial and is not recommended. Additional supportive therapies should be aimed at controlling the lactic acidosis, seizures, and hemodynamic compromise.

Specific antidotes, such as sodium nitrite and sodium thiosulfate, are available for treatment of cyanide poisoning. Sodium nitrite oxidizes hemoglobin to form methemoglobin.[1] Cyanide binds preferentially to methemoglobin rather than the ferric iron of the cytochrome in the mitochondria. Thus methemoglobin effectively removes cyanide from the extracellular space, displacing cyanide from the cytochrome in the intracellular fluid.[1] The net effect improves both cellular respiration and function. Cyanide eventually dissociates from methemoglobin and is converted to thiocyanate. Thus the second antidote, sodium thiosulfate, is given to augment the systemic clearance of cyanide by serving as a sulfur donor for the conversion of cyanide to thiocyanate.[1] Thiocyanate is then excreted in the urine (see Figure 86-1).[1,3] Adverse effects of sodium nitrite therapy include vasodilation and hypotension. Although methemoglobin is the desired end point of therapy, it may exacerbate hypoxemia in smoke inhalation victims with simultaneous methemoglobinemia carbon monoxide toxicity. Therefore nitrites should be avoided in smoke inhalation victims because of the risk of worsening the oxygen carrying capacity deficit.[1]

An additional proposed treatment strategy for patients with cyanide poisoning is hydroxycobalamin (vitamin B_{12A}). Hydroxycobalamin binds free cyanide, forming cyanocobalamin.[6] Cyanocobalamin is then excreted in the urine. The principal toxic effect of hydroxycobalamin is a reddish discoloration of the skin and mucous membranes.[6]

In a dog model of cyanide poisoning, only dogs that received sodium nitrite, thiosulfate, or hydroxycobalamin before and during infusions of potassium cyanide survived. However, hydroxycobalamin should be used with caution as a sole therapy because declines in the blood pressure and the heart rates of dogs were greater than those seen in the groups receiving sodium nitrite and thiosulfate.[6] Therefore recommendations for antidote treatment of cyanide poisoning include the administration of 5 mg/kg bolus of 3% sodium nitrite (30 mg/ml) slowly over 15 minutes, followed by a bolus or constant rate infusion of 25% sodium thiosulfate at 150 to 500 mg/kg.[3,11] If the clinical response is inadequate after 30 minutes, a second dose of both sodium nitrite and sodium thiosulfate at half the original dose may be administered. Methemoglobin levels ideally should be monitored with co-oximetry and maintained at less than 40% (Table 86-1).[7] An adequate clinical response to antidote therapy is defined as a return of consciousness, spontaneous respiration, and stable vital signs.[8]

Table 86-1 Treatment of Cyanide Poisoning

Treatment	Dosage
Supplemental oxygen	100%
3% Sodium nitrite*	5 mg/kg IV bolus over 15 minutes†
25% Sodium thiosulfate	150 to 500 mg/kg IV bolus or constant rate infusion
Hydroxycobalamin	75 to 150 mg/kg IV bolus or 25 mg/hr in patients with sodium nitroprusside toxicity

Hydroxycobalamin (75 to 150 mg/kg as a bolus or 25 mg/hr in sodium nitroprusside toxicity) may be considered as an additional treatment, especially in fire victims who already have a reduced concentration of functioning hemoglobin, and sodium nitrite therapy is contraindicated (see Table 86-1).[3,6,7]

[*] Should not be administered to victims of smoke inhalation.

[†] Both sodium nitrite and sodium thiosulfate may be repeated at half of the original dose if clinical response is not achieved in 30 minutes.

86.7 SODIUM NITROPRUSSIDE

As stated previously, sodium nitroprusside therapy can involve significant risk for cyanide toxicity. Sodium nitroprusside is comprised of a ferric iron center complexed with five cyanide moieties.[3] Once infused, sodium nitroprusside dissociates spontaneously to form methemoglobin, nitric oxide, and cyanide. Cyanide may then react with methemoglobin to form cyanomethemoglobin.[3] When sodium nitroprusside infusions exceed 2 µg/kg/min, or when sulfur donors and methemoglobin are exhausted, cyanide may accumulate, leading to toxicity.[3] Regardless of the infusion rate or duration, any patient receiving sodium nitroprusside therapy who exhibits central nervous system signs, cardiovascular instability, and an increasing metabolic acidosis should be assessed for cyanide toxicity. Sodium nitroprusside should be discontinued and treatment for cyanide toxicity instituted.[3]

86.8 SUGGESTED FURTHER READING[*]

KJ Drobatz, LM Walker, JC Hendricks: Smoke exposure in cats: 22 cases (1986–1997). *J Am Vet Med Assoc*. **215**, 1999, 1312, *A retrospective case series of 22 cats exposed to fires and admitted to an urban veterinary teaching hospital*.

KJ Drobatz, LM Walker, JC Hendricks: Smoke exposure in dogs: 27 cases (1988-1997). *J Am Vet Med Assoc*. **215**, 1999, 1306, *A retrospective study evaluating the clinical findings, prognostic variables, and clinical course of 27 dogs exposed to smoke and admitted to an urban veterinary teaching hospital*.

R Gracia, G Shepherd: Cyanide poisoning and its treatment. *Pharmacotherapy*. **24**, 2004, 1358, *This paper is the most current review in the medical literature of cyanide poisoning and its treatment*.

AA Salkowski, DG Penney: Cyanide poisoning in animals and humans: a review. *Vet Hum Toxicol*. **36**, 1994, 455, *The most comprehensive review currently available of experimental studies of cyanide poisoning in animals*.

[*] See the CD-ROM for a complete list of references

87 Chapter 87 Carbon Monoxide

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87.1 KEY POINTS

- Carbon monoxide toxicity can occur following inhalation of fumes produced by incomplete combustion of hydrocarbons in fires, car exhaust systems, charcoal grills and gasoline-powered generators, broilers, and heating systems.
- The exact mechanism of carbon monoxide toxicity is still under investigation, but is thought to be due to both tissue hypoxia and cellular toxicity.
- Signs of carbon monoxide toxicity initially include neurologic depression, vomiting, tachycardia, tachypnea, and cherry red mucous membranes. Delayed neurologic abnormalities following initial recovery have been reported in humans, dogs, and cats.
- Confirmation of carbon monoxide toxicity is performed via measurement of carboxyhemoglobin with a co-oximeter.
- Treatment of carbon monoxide toxicity involves 100% oxygen therapy and supportive care.

87.2 INTRODUCTION

Carbon monoxide is a colorless, odorless, nonirritating gas that is produced by incomplete combustion of hydrocarbons in fires, car exhaust systems, charcoal grills, and gasoline- powered generators, broilers, and heating systems.[1-3] In fires it can be produced by the incomplete combustion of common substances such as wood, cotton, paper, polyvinyl chloride, and polystyrene.[4] Carbon monoxide is produced endogenously as an end product of erythrocyte and heme catabolism, and in the central nervous system (CNS) as a neurotransmitter.[5-7] It is ubiquitous in the environment, with a typical concentration in the atmosphere of less than 0.001%.[1] As a result of endogenous production of carbon monoxide and its presence in air, normal individuals have carboxyhemoglobin (COHb) levels of 1% to 3% (although higher levels have reported in cats).[1]

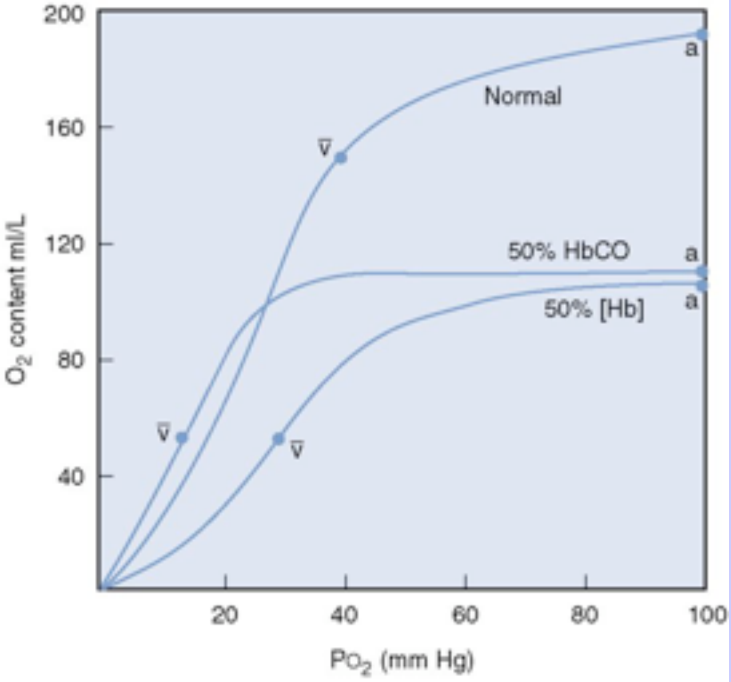
Inhalational intoxication from accidental or intentional exposure to carbon monoxide is one of the most common life-threatening toxicities in humans.[1,7] Inhalation of air with 0.1% carbon monoxide can result in COHb levels in excess of 50%.[2] In small animal veterinary patients, the reported causes of carbon monoxide toxicity include smoke inhalation,[8-10] gas broilers or heaters,[11-15] and a running generator.[2]

87.3 PATHOPHYSIOLOGY

87.3.1 Absorption

Carbon monoxide is absorbed rapidly through the lungs at the level of the alveolus.[1] The quantity of gas absorbed is dependent on minute ventilation (the product of respiratory rate and tidal volume), duration of exposure, and the concentration of carbon monoxide in the environment.[1] Once absorbed into the blood and circulated throughout the body, a small amount of carbon monoxide is oxidized to carbon dioxide, some remains as gas in solution, and some binds to heme proteins including hemoglobin, myoglobin, and cytochrome a_3 in mitochondria.[1,4] Studies indicate that the binding of carbon monoxide to heme proteins and its presence in plasma result in different aspects of its toxicity. The pathophysiology of carbon monoxide toxicity involves two main mechanisms: impaired oxygen delivery to tissues (hypoxia) and direct cellular toxicity.[1,2,4,7,10]

Figure 87-1 A comparison of oxygen content of the blood based on the partial pressure of oxygen in various scenarios: normal, anemia with a 50% reduction in hemoglobin (50% [Hb]), and a carboxyhemoglobin level of 50% (50% HbCO). Both anemia and carboxyhemoglobin result in a significant decrease in the oxygen-carrying capacity of the blood. From Berne RM, Levy MN, Koeppen BM, Stanton BA, editors: *Physiology,* ed 5, St Louis, 2005, Mosby.



87.3.2 Hypoxic Toxicity

The hypoxic mechanism of carbon monoxide toxicity involves the interaction of carbon monoxide with hemoglobin in the blood: carbon monoxide displaces oxygen from hemoglobin and causes an allosteric hindrance of oxygen release from hemoglobin to the tissues.[4,16] The resultant tissue hypoxia results in cellular shock, CNS depression, and cardiovascular compromise.

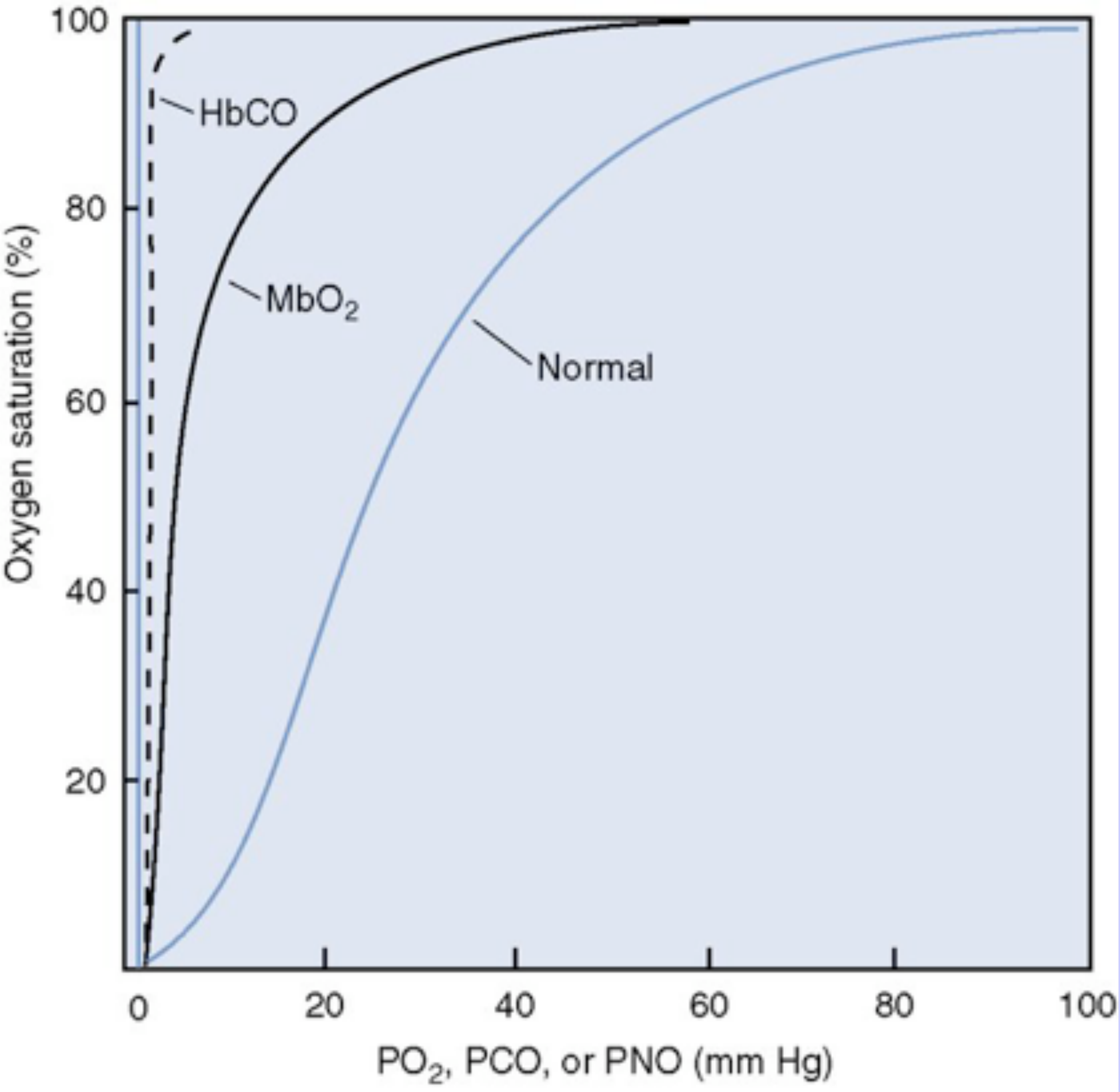
Carbon monoxide competes with oxygen for hemoglobin binding sites with 200 to 250 times the affinity.[1,16] Carbon monoxide binds two of the four available heme groups in each molecule of hemoglobin, causing a decrease in the oxygen carrying capacity of 50% (Figure 87-1) and shifting the oxyhemoglobin dissociation 369 curve down.[16,17] Thus very low levels of carbon monoxide in the blood result in markedly reduced oxygen 370 carrying capacity despite a normal hemoglobin concentration and normal partial pressure of oxygen.

The dissociation of oxygen from hemoglobin is also affected by carbon monoxide, which binds tightly to hemoglobin, markedly disturbing the chemical equilibrium of the molecule.[16,17] The change in equilibrium of the COHb results in an interference with both the association and dissociation of oxygen.[16] Therefore oxygen bound to hemoglobin, which is also bound to carbon monoxide is not easily released to the tissues, and the oxyhemoglobin dissociation curve is shifted to the left (Figure 87-2).[16,17] Decreased release of oxygen to the tissues exacerbates the cellular hypoxia caused by decreased oxygen content and subsequent delivery.

87.3.3 Cellular Toxicity

Hypoxia alone, however, does not explain the variation in individual response to a given level of COHb and the delayed neurologic syndrome associated with carbon monoxide toxicity. Studies have demonstrated cerebral hyperemia, tachycardia, and tachypnea during carbon monoxide toxicity, representing a compensatory mechanism to maintain oxygenation in the face of decreased oxygen carrying capacity.[1,7,18] Therefore the brain does not commonly suffer from hypoxia during carbon monoxide toxicity unless there is accompanying cardiovascular dysfunction or severely elevated levels of COHb (>70%), overwhelming the adaptive response.[7,18] A study was performed comparing the clinical signs of dogs subjected to inhaled carbon monoxide with dogs bled to a hematocrit of approximately 25% and subsequent volume replacement with crystalloid and colloid fluids or COHb-containing red blood cells.[19] The dogs subjected to inhaled carbon monoxide achieved COHb levels of 54% to 90% and died. The dogs bled to an anemic state and given COHb-containing red blood cells to achieve a COHb level of 60% survived indefinitely with an outcome similar to that of dogs who were bled and received volume replacement with crystalloid and colloid solutions.[19] This study confirmed the suspicion that a mechanism other than hypoxia from high levels of COHb results in toxicity. This mechanism is thought to be the consequence of cellular toxicity.[2,4,7,19] Cellular toxicity associated with carbon monoxide poisoning appears to involve both direct and indirect mechanisms.

Figure 87-2 Oxygen saturation curves of hemoglobin, carboxyhemoglobin, and myoglobin. Note the leftward shift of the carboxyhemoglobin curve denoting a decreased release of oxygen to the tissues. From Berne RM et al, editors: *Physiology,* ed 5, St Louis, 2005, Mosby.



87.3.3.1 Direct Mechanisms

Direct cellular toxicity can be due to carbon monoxide binding to the heme proteins myoglobin and cytochrome a_3 in the electron transport chain of mitochondria. Carbon monoxide binds to myoglobin in cardiac and skeletal muscle, potentially causing decreased contractile function of the muscle cells.[4,20] Oxygen has a greater affinity for myoglobin than carbon monoxide, however, and pathologic effects of carbon monoxide binding to myoglobin are thought to be minimal unless there is associated tissue hypoxia.[7] Tissue hypoxia may be caused by the effects of carbon monoxide on oxygen delivery, depression of the CNS with resultant apnea, and decreased effective cellular respiration due to binding of carbon monoxide to cytochrome a_3. Myocardial depression occurs as a direct result of mitochondrial dysfunction and may result in decreased cardiac output, contributing further to tissue hypoxia.[20]

87.3.3.2 Indirect Mechanisms

There is a growing body of evidence demonstrating indirect mechanisms through which carbon monoxide toxicity results in changes that lead to cellular toxicity, particularly within the brain. These changes include sequestration of leukocytes,[7] increased nitric oxide (NO) production,[7,21,22] reperfusion injury,[1,7] lipid peroxidation,[1,7,23] and direct neurotoxicity from carbon monoxide activity as the a neurotransmitter.[6,7]

It has been demonstrated experimentally that carbon monoxide activates polymorphonuclear leukocytes (PMNLs), resulting in diapedesis and leukoencephalopathy.[7] The activated neutrophils can contribute to tissue damage by producing reactive oxygen species, releasing proteolytic enzymes, and obstructing capillaries as the PMNLs accumulate.[24] NO levels increase during exposure to high levels of carbon monoxide as a result of increased NO release from platelets[21] and production in neuronal tissue.[7,22] NO may have both a protective and damaging role in carbon monoxide toxicity. NO decreases PMNL adhesion to endothelium, and a transient rise in nitric oxide may protect brain tissue initially, although falling levels may be responsible for the delayed neurologic sequelae seen in some cases.[21] The combination of NO and superoxide (one of the reactive oxygen species produced in activated PMNLs and other cells during reperfusion), however, results in peroxynitrite production, a key player in lipid peroxidation.[24] Lipid peroxidation is a process characterized by conversion of membrane lipids to reactive species and propagation of oxidative damage, culminating in severely damaged or destroyed cell membranes.[24] Thus elevated carbon monoxide levels set up a chain reaction resulting in direct tissue damage, reperfusion injury, lipid peroxidation, cellular dysfunction, and ultimately cell death within the brain.[7,23]

The role of endogenous carbon monoxide as a neurotransmitter and the potential implications of exogenous carbon monoxide overstimulating certain neural functions are being explored.[6,7] An altered ratio of carbon monoxide and NO may exaggerate neurologic malfunction.[7]

87.3.4 Narcotizing Effect

The mechanism of CNS depression in patients with carbon monoxide exposure is still essentially unknown. It has been established experimentally that there is a decrease in oxygen consumption by the brain, an observation thought to be associated with the narcotizing effect of carbon monoxide.[18] Cerebral vasodilation due to elevated carbon monoxide levels may cause cerebral hyperemia, increased intracranial pressure, and edema.[1] Carbon monoxide affects neural function through its actions as a neurotransmitter and causes derangements in dopaminergic and serotonergic neural pathways.[7] These changes are theoretically involved in the mentation changes associated with carbon monoxide exposure.

87.4 CLINICAL SIGNS

87.4.1 Initial Clinical Signs

The clinical signs of carbon monoxide toxicity initially reflect the gas's effect on the CNS. These are lethargy, depression, headache, confusion, syncope, seizures, unconsciousness, and death.[1,2] Concurrent signs reported at the onset of toxicity also include tachypnea, tachycardia, nausea, vomiting, and cherry red mucous membranes.[1,2] Arrhythmias may occur as a result of myocardial toxicity.[1] The classic cherry red mucous membranes are indicative of the color of COHb and reported to occur only rarely in humans.[1,2] Hyperemic mucous membranes were reported in 7 of 24 dogs and 2 of 17 cats in retrospective analyses of smoke inhalation.[8,9] Unfortunately, COHb levels in these cases were not available, making it difficult to determine whether or not hyperemic mucous membranes represented elevated COHb or vasodilation from other causes. Hypotension is reported to occur rarely in experimental cases of carbon monoxide toxicity.[23] If carbon monoxide toxicity occurs concurrently with smoke inhalation, symptoms may include those referable to direct respiratory system damage such as dyspnea, cyanosis, and upper airway obstruction.

Severity of signs ranges from mild to severe and does not correlate consistently with COHb levels.[1] Generally, however, COHb levels over 15% result in overt signs of toxicity such as tachypnea and headache, over 30% in neurologic dysfunction, and levels 50% or more typically result in loss of consciousness that can progress to apnea and death.[4] Increased duration of exposure to elevated levels of carbon monoxide contributes to morbidity.[1]

87.4.2 Delayed Neurologic Sequelae

A syndrome known as delayed neuropsychiatric syndrome (DNS) has been described in humans who have suffered carbon monoxide toxicity. Clinical signs develop 3 to 240 days following the toxic episode and include cognitive and personality changes, incontinence, dementia, parkinsonism, gait disturbance, hearing loss, and psychosis.[1,2,10] The reported incidence of DNS varies but is approximately 10% to 30%.[1,2] Incidence of DNS increases to 25% to 50% in patients who suffered loss of consciousness or with COHb levels over 25%.[25] Approximately 50% to 75% of humans who suffer from DNS recover within 1 year.[1,2] Risk factors for DNS include age (older), duration of unresponsiveness, and history of illness.[2,10] Hypoxia alone is considered unlikely to cause these changes.[7,10] The precise mechanism of DNS is unclear, but contributing factors are thought to include a compromise of autoregulation of brain blood flow resulting in hypoxia, followed by oxidative damage and lipid peroxidation.[1,2,7]

Delayed neurologic sequelae have been reported in animals following smoke inhalation and carbon monoxide intoxication.[2,10,26] Clinical signs range from an ataxic gait to inability to ambulate, depressed to stuporous mentation, and dysacousis (deafness).[2,10] One retrospective analysis of 11 dogs with neurologic signs associated with smoke inhalation noted a 46% occurrence of initial improvement in clinical signs followed by acute recurrence of neurologic dysfunction 2 to 6 days after the insult.[26]

87.5 DIAGNOSIS

Initial sign of carbon monoxide toxicity such as depression, tachypnea, and tachycardia can be nonspecific, particularly if they are mild. Historical information and clinical suspicion are therefore vital to the diagnosis in small animals.

87.5.1 Co-oximetry

Definitive diagnosis of carbon monoxide toxicity involves direct measurement of COHb levels. This is performed with a co-oximeter, a machine used to measure hemoglobin content, oxygen saturation, percentage of COHb, and percentage of methemoglobin.[2] Arterial samples are ideal for analysis of acid-base status and partial pressure of oxygen, but venous samples are adequate for determination of COHb levels.

In some cases, particularly if the animal received supplemental oxygen during transport, the COHb level may have fallen and may even be normal at the time of presentation. Diagnosis in these cases is based on clinical signs and a history suggestive of carbon monoxide toxicity.[1]

87.5.2 Pulse Oximetry

It has been well documented that pulse oximetry is inaccurate in cases of carbon monoxide toxicity and will be falsely elevated, a phenomenon known as the *pulse oximetry gap*. [1,2,27] The principle of pulse oximetry is based on measurement of the ratio of light absorbed by tissues at a red wavelength (660 nm) to that at an infrared wavelength (940 nm).[27] This absorption ratio reflects the arterial oxygen saturation through calibration curves that have been previously established.[27] These calibration curves, however, do not account for variant hemoglobin species such as COHb and measure only oxyhemoglobin and deoxyhemoglobin. COHb and oxyhemoglobin have similar light absorptions at the red wavelength[27] and are therefore indistinguishable by the pulse oximeter. However, the COHb cannot achieve an oxygen saturation of greater than 50%, resulting in a falsely normal pulse oximetry reading when the actual percentage of oxyhemoglobin is low. The pulse oximetry 371

372 gap is defined as the difference between percentage of saturation measured by a pulse oximeter and the actual oxyhemoglobin saturation. A retrospective analysis of human patients with carbon monoxide toxicity demonstrated a correlation between the pulse oximetry gap and COHb levels.[27] Therefore, if a blood gas analyzer that uses spectrophotometry is available to measure oxygen saturation, the percentage of COHb can be approximated throughout treatment with repeated measurements of oxygen saturation using a blood gas machine and routine pulse oximetry.

87.5.3 Blood Gas Analysis

Blood gas analysis is useful in cases of carbon monoxide toxicity to evaluate patients for metabolic acidosis, suggesting decreased perfusion, a respiratory acidosis or alkalosis indicative of hypoventilation or hyperventilation, respectively, and arterial partial pressure of oxygen (PaO_2) measurements. One must keep in mind, however, that the oxygen-hemoglobin dissociation curve has been shifted down and to the left (see Figures 87-1 and 87-2), so PaO_2 does not reflect typical oxyhemoglobin levels but rather the amount of oxygen dissolved in the blood. One of the main indications for measuring PaO_2 levels in these patients is to assess the efficacy of oxygen therapy in maintaining supranormal PaO_2 levels to decrease the half-life of carbon monoxide (see Oxygen Therapy). Lactate levels may also be useful in assessing tissue oxygenation.

87.5.4 Neurologic Evaluation

Once the diagnosis of carbon monoxide toxicity has been established, a full baseline neurologic examination and frequent reevaluation should be performed to determine the appropriate aggressiveness of treatment (see Treatment) and track progression of neurologic sequelae.

87.6 TREATMENT

87.6.1 Oxygen Therapy

Elimination of carbon monoxide depends on minute ventilation, duration of exposure, and the fraction of inspired oxygen.[1] Oxygen therapy is the mainstay of treatment for carbon monoxide toxicity, because increasing the amount of oxygen in the blood decreases the half-life of carbon monoxide as dissolved oxygen competes with carbon monoxide for hemoglobin binding sites.[1,2] Carbon monoxide is then displaced from hemoglobin and exhaled through the lungs. In humans, the half-life of carbon monoxide is 4 to 6 hours when the patient is breathing room air (fractional inspired oxygen of 21%) and 40 to 80 minutes with 100% oxygen therapy.[1,3] Theoretically, animals who have suffered smoke inhalation and have comorbid pulmonary disease can have a longer carbon monoxide half-life, because they can not blow off the gas normally. However, a retrospective study looking at carbon monoxide half-life in humans who had suffered carbon monoxide toxicity demonstrated no difference in the half-life of carbon monoxide between those who had experienced smoke inhalation and those who had not.[3] Oxygen therapy is also indicated to prevent DNS, because the mechanism of this disorder is thought to be related to hypoxia and reperfusion. Limiting the degree and duration of hypoxia has become the goal of treatment to prevent DNS.[2]

Hyperbaric oxygen (HBO) therapy is used in severe human cases of carbon monoxide toxicity because it may decrease the incidence of DNS.[25] HBO is useful because it increases the amount of dissolved oxygen in the blood, so that the half-life of carbon monoxide is shorter than with normobaric oxygen therapy, and less carbon monoxide binds to heme proteins because the oxygen competes for binding sites.[25] The half-life of carbon monoxide when breathing hyperbaric oxygen at 2 atmospheres of pressure is only 15 to 30 minutes.[1] Data on the beneficial effects of HBO are conflicting, and it may offer no significant benefit over normobaric oxygen therapy.[1,25] A prospective, randomized clinical trial comparing the effects of hyperbaric and normobaric oxygen therapy demonstrated a reduced frequency of occurrence of DNS by 46% in patients treated with hyperbaric oxygen.[25]

In veterinary patients, HBO is not a practical option. Therefore therapy with 100% oxygen to maximize PaO_2 using an oxygen cage or intubation and mechanical ventilation in those with significant pulmonary pathology is recommended until the COHb is normal (<3%). Based on rodent studies, it has been recommended that the doctor attempt to maintain a PaO_2 of at least 300 mm Hg to theoretically inhibit diapedesis of PMNLs and resultant brain lipid peroxidation.[2] Clinical human and experimental literature indicate that this goal should achieve rapid elimination of carbon monoxide and may minimize DNS, but it has not been effective in experimental or clinical studies in dogs and cats.

87.6.2 Supportive Care

Other than oxygen therapy, the bulk of treatment for moderate to severe cases of carbon monoxide toxicity is supportive care. Cardiovascular monitoring and other measures as indicated to ensure adequate tissue perfusion are necessary.

87.6.3 Other Treatment Strategies

A recent case series used Oxyglobin, a bovine hemoglobin-based oxygen carrier (HBOC), in five animals with carbon monoxide toxicity in order to elevate the hemoglobin level of the blood and therefore increase oxygen carrying and delivering capacities.[2] The animals improved clinically more rapidly than one would expect given the half-life of carbon monoxide.[2] HBOC offers other potential benefits to patients suffering from carbon monoxide toxicity, namely, the strong colloidal effect of these solutions and their interference with NO–mediated vasodilation.[2,28] The strong colloi-dal effect may help reduce cerebral edema and increase intravascular volume, augmenting perfusion. These solutions should be used with caution, however, in animals with pulmonary edema secondary to smoke inhalation, because colloids may exacerbate edema in the presence of damaged pulmonary endothelium. The mechanism of interference with nitric oxide function is uncertain, but is thought to involve either scavenging of NO or physical obstruction of its interaction with guanylate cyclase, the reaction that triggers vasodilation.[28] Although not discussed as a possible benefit in the case series using HBOC in carbon monoxide toxicity in dogs and cats,[2] the effects of HBOC on NO could theoretically benefit or harm the carbon monoxide victim. 372 373 Scavenging nitric oxide may be beneficial in preventing some of the sequelae of carbon monoxide toxicity (see earlier discussion on the role of NO in carbon monoxide toxicity), although vasoconstriction due to decreased NO activity could result in decreased tissue perfusion.

There is one published report of the use of antioxidants including N-acetylcysteine and vitamin E to treat smoke inhalation and presumed carbon monoxide toxicity in veterinary medicine.[10] These modalities were employed in a case of DNS to prevent lipid peroxidation from occurring within the brain.[10] The dog's neurologic function improved to almost normal within 1 week and to completely normal after 14 days, indicating a potential beneficial effect of the antioxidant therapy. With the recovery rate from DNS being 50% to 75% in humans[1,2]; however, it is difficult to know how much the antioxidants contributed to this dog's recovery. The effectiveness of antioxidant therapy in preventing brain damage in cases of carbon monoxide toxicity is unknown.

87.7 PROGNOSIS

The prognosis for small animal patients with carbon monoxide toxicity in is hard to determine given the relatively small number of published cases of verified toxicity in dogs and cats. Initial unconsciousness or severe neurologic abnormalities seem to be associated with a more guarded prognosis in both the human and veterinary literature. The published retrospective analysis evaluating clinical course and mortality in dogs that had suffered smoke inhalation and had neurologic signs noted that mortality due to death or euthanasia was 60% in the dogs with delayed neurologic signs as opposed to 46% in dogs without recurrence of neurologic signs.[26] One veterinary case report; however, indicated an 83% survival in the case of six animals[2] with carbon monoxide toxicity. Complete recovery following recurrence of significant neurologic abnormalities was also reported in one dog that had been in a fire.[10] Extrapolation from the human literature, as well as cases presented in the veterinary literature, indicate that the overall prognosis is fair with time and supportive care.

87.8 SUGGESTED FURTHER READING*

AC Berent, J Todd, J Sergeeff, et al.: Carbon monoxide toxicity: a case series. *J Vet Emerg Crit Care*. **15**, 2005, 128, *A small animal case series of known carbon monoxide toxicity with a detailed discussion section providing a review in the veterinary literature*.

TK Day: Current development and use of hemoglobin-based oxygen-carrying (HBOC) solutions. *J Vet Emerg Crit Care*. **13**, 2003, 77, *A review paper reporting the various HBOC solutions, their indications, and their effects in both clinical human medicine and veterinary medicine*.

SR Sharar, LD Hudson: Toxic gas, fume, and smoke inhalation. In JE Parrillo, RP Dellinge (Eds.): *Critical care medicine: Principles of diagnosis and management in the adult*. ed 2, 2001, Mosby, St Louis, *A chapter in the pulmonary section of this human critical care text that gives an excellent overview of smoke inhalation injury, the toxins involved, clinical signs, and treatment*.

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* See the CD-ROM for a complete list of references

88 Chapter 88 Methemoglobinemia

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88.1 KEY POINTS

- Methemoglobin (metHb) is hemoglobin in which the ferrous (Fe^{2+}) molecule is oxidized to the ferric (Fe^{3+}) form. MetHb is incapable of carrying oxygen, and high levels (>20%) can cause cellular hypoxia and shock.
- Clinical methemoglobinemia occurs when erythrocyte defense systems are overwhelmed and cannot reduce metHb back to hemoglobin fast enough to keep up with the oxidative damage MeTHbreductase deficiency is a rare condition in small animals that leads to inefficient reduction of metHb in the body, but may or may not lead to clinical signs of methemoglobinemia.
- Substances that can cause clinical methemoglobinemia in small animals include acetaminophen, topical benzocaine formulations, phenazopyridine (a urinary tract analgesic), nitrites, nitrates, and skunk musk.
- Many substances that cause methemoglobinemia can also cause the body to form clinically significant numbers of Heinz bodies (HzBs), aggregations of denatured hemoglobin that can lead to red blood cell destruction and anemia.
- Treatment for methemoglobinemia involves augmentation of endogenous glutathione with N-acetylcysteine (NAC), antioxidant therapy, increased clearance or decreased metabolism of a toxin, blood transfusion if required, and supportive care.

88.2 INTRODUCTION

Hemoglobin, the molecule that confers gas-carrying capacity to erythrocytes, is composed of four polypeptide chains (globins); each is attached to a heme molecule.[1,2] Heme is made up of a tetrapyrrole with a central iron molecule.[1,2] The iron molecule must be maintained in the ferrous (Fe^{2+}) state in order for the hemoglobin to bind oxygen.[1-4] MetHb is an inactive form of hemoglobin created when the iron molecule of hemoglobin is oxidized to the ferric (Fe^{3+}) state because of oxidative damage within the red blood cell.[1-4] It gives the red blood cell a darker brown color and results in dusky cyanotic or chocolate-colored mucous membranes.[1,2] MetHb increases the affinity for oxygen in the remaining ferrous moieties of the hemoglobin molecule, decreasing release of oxygen to the tissues and shifting the oxyhemoglobin dissociation curve to the left.[5,6] Approximately 0.5% to 3% of hemoglobin is oxidized to metHb q24h in normal animals.[2-4] There are numerous mechanisms to prevent oxidative injury in erythrocytes, however, and metHb is reduced back to functional hemoglobin rapidly such that metHb accounts for less than 1% of total hemoglobin in normal adults.[2,3] Exogenous substances that overwhelm the antioxidant defenses, or a congenital or acquired abnormality within the adaptive response, can result in elevated levels of metHb.

88.3 PATHOPHYSIOLOGY

88.3.1 Oxidation in the Erythrocyte

Reactive species derived from oxygen can cause oxidative damage within the body by transferring or extracting an unpaired electron to or from another molecule. Protective mechanisms that prevent or reverse oxidative damage include proteins that act as free radical scavengers and reducing agents that can remove the unpaired electron from an oxidized molecule.

Erythrocytes are especially vulnerable to oxidative damage because they carry oxygen, are exposed to various chemicals in plasma, and have no nucleus or mitochondria.[1,3] The lack of cellular organelles renders the membrane the deformability necessary to navigate capillary beds, but results in a cell that is incapable of producing proteins or performing efficient energy production.[1] They therefore have a finite number of cell proteins and are reliant on anaerobic respiration to generate energy and reducing agents.[1] Oxidants continuously generated in vivo include hydrogen peroxide (H_2O_2), superoxide free radicals (O_2^-), and hydroxyl radicals (OH·) (Box 88-1).[1,3,4] Hemoglobin can undergo autooxidation as an electron is pulled off the hemoglobin onto an oxygen molecule, resulting in the generation of metHb and O_2^-.[1,3] Free radicals may also extract electrons by oxidizing deoxyhemoglobin.[3] In contrast oxidant toxins can donate an electron to oxyhemoglobin, creating metHb and hydrogen peroxide (Box 88-1).[3]

Despite their limited capacity to produce energy and proteins, erythrocytes have many mechanisms to protect themselves from oxidative damage. These include superoxide dismutase, catalase, glutathione peroxidase, glutathione, and metHb reductase (cytochrome b_5 reductase) (see Box 88-1).[1,3] Glutathione is a tripeptide produced in erythrocytes and composed of glutamic acid, cysteine, and glycine and contains an easily oxidizable sulfhydryl (SH) group.[3] It is a powerful antioxidant that operates as a free radical scavenger. Reducing agents such as nicotinamide adenine dinucleotide phosphate (NADPH) and nicotinamide adenine dinucleotide (NADH) are instrumental in reducing oxidized glutathione and metHb back to functional molecules (see Box 88-1).[1,3,4]

88.3.2 Heinz Bodies

Heinz bodies (HzBs) are aggregates of denatured precipitated hemoglobin within erythrocytes that form as hemoglobin that has undergone oxidative damage is metabolized.[1-4] Oxidation of the SH groups of hemoglobin, either through autooxidation, free radical extraction of an electron, or oxidant toxin donation of an electron, causes conformational changes in the globin chains that results in precipitation of the denatured globin.[3,4] Aggregates of denatured globin and metabolized metHb clump into HzBs and continue to coalesce until visible, pale structures can be seen within the red blood cell cytoplasm (see Color Plate 88-2, *B*).[4] The complete sequence of events necessary for HzB formation is still being elucidated, but it is thought that formation of metHb is necessary for the development of HzBs.[3] Feline hemoglobin is more susceptible to oxidative damage 374 375 because it has eight SH groups on the globin part of the molecule rather than four, as the canine counterpart does.[3,4,7,8]

88.3.2.1 Box 88-1 Chemical Reactions Resulting in Free Radical Formation, Their Removal, and Methemoglobin Reduction

88.3.2.1.1 Free Radical Formation

Superoxide anion: $O_2 + e^- \rightarrow O_2^-$

Ferric production: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3} + OH^- + OH^{\cdot}$

88.3.2.1.2 Mechanisms of Free Radical Removal

Superoxide dismutase reaction: $2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$

Catalase reaction: $O_2^- + H_2O_2 \rightarrow O_2 + OH^- + OH^{\cdot}$

88.3.2.1.3 Glutathione Peroxide and Glutathione Reductase Reactions

$H_2O_2 + 2\,GSH \xrightarrow{GP} 2\,H_2O + GSSG$

$GSSG + H^+ + NADPH \xrightarrow{GR} 2\,GSH + NADP^+$

88.3.2.1.4 Methemoglobin Reduction

$MetHb - Fe^{3+} \xrightarrow{MR} HbFe^{2+} + O_2$

NADH NAD$^+$

CAT, Catalase; *GP,* glutathione peroxidase; *GR,* glutathione reductase; *GSH,* glutathione; *GSSG,* oxidized glutathione; *HbFe*$^{2+}$*,* ferrous hemoglobin; *MR,* methemoglobin reductase; *NAD,* nicotinamide adenine dinucleotide; *NADH,* nicotinamide adenine dinucleotide; *NADPH,* nicotinamide adenine dinucleotide phosphate; *SOD,* superoxide dismutase.

Modified from Engelking LR: *Textbook of veterinary physiological chemistry,* Jackson Hole, WY, 2004, Teton NewMedia.

HzBs have an affinity for membrane proteins.[4] Binding of a HzB to these proteins causes disruption of anion transport, decreased membrane deformability, and aggregations of membrane protein complexes that may act as autoantibodies.[4,7] Numerous HzBs can disrupt the membrane sufficiently to result in "ghost" cells, empty red blood cells with just a cell membrane and HzB remaining, which are associated with oxidation-induced intravascular hemolysis.[7] More commonly, however, erythrocytes that have undergone oxidative damage are removed by the mononuclear phagocyte system, particularly within the spleen.[7] Rigid cells or cells with large

HzBs protruding from the surface will become lodged in the narrow openings between splenic endothelial cells and undergo phagocytosis by the splenic macrophages.[3] In most animals, the spleen can perform pitting functions and remove the HzBs from the erythrocyte.[3] Feline spleens, however, have an ultrastructural variation and impaired ability to catch and remove oxidized red blood cells.[9] As a result of the combination of more SH groups available for oxidation on feline hemoglobin and the unique spleen in this species, healthy cats often have notable HzBs in circulation (with reports up to 96%).[9] The reasons that some cats undergo hemolysis with HzB percentages lower than 96% but other cats will have no clinical signs with most of their erythrocytes affected are still unknown.[7,9] It is clear, however, that various agents induce oxidative damage in different ways and to varying extents, and the nature of the damage, the amount of affected hemoglobin within a cell, and individual variations seem to determine whether a given cat will develop clinically significant hemolysis.[7]

88.4 SPECIFIC CAUSES OF ERYTHROCYTE OXIDATION

Methemoglobinemia has been documented in small animals in association with acetaminophen ingestion, topical benzocaine products, phenazopyridine (a urinary tract analgesic) products, nitrites, nitrates, skunk musk,[10] and metHb reductase deficiency.[3,4] Agents that have resulted in metHb in humans and may be used in veterinary medicine include dapsone, nitroglycerin, and nitroprusside.[11] Regardless of the toxic agent, metHb is often formed within minutes to hours of exposure. Substances that cause metHb production are likely to cause HzB production and potentially hemolytic anemia in the days following the exposure. Numerous substances that cause an increase in HzBs are thought to cause some degree of methemoglobinemia, but associated clinical signs are typically attributable to a hemolytic anemia secondary to the HzBs rather than the metHb. These substances include *Allium* plants (onions and garlic), propylene glycol, zinc, methylene blue, crude oils, naphthalene (ingredient in moth balls),[12] repeated use of propofol in cats,[9] phenothiazine, phenylhydrazine, methionine (a urinary acidifier) in cats, menadione (vitamin K_3) in dogs, and copper (particularly in animals with copper storage diseases).[3,4] Depending on the individual patients' metabolism, the dose, and the period over which it was ingested, these substances will cause varying degrees of HzB formation, and anemia does not usually occur until HzB formation is moderate to severe.

88.4.1 Acetaminophen

Acetaminophen (Tylenol) (see Chapter 79, Acetaminophen) is an analgesic and antipyretic drug that is used widely in human medicine.[5,8] It is present in many pain and cold medications.[5] Although considered safe in humans, this drug can be toxic to small animals, causing acute hepatoxicity in dogs and life-threatening methemoglobinemia in cats.[5,8] Most phenacetin, a component of over-the-counter drug formulations, is metabolized rapidly to acetaminophen and could result in toxicity in small animals.[5] A dose of as little as 10 mg/kg of acetaminophen is toxic for cats, and 150 to 200 mg/kg is toxic for dogs.[5] Unfortunately, the vast majority of acetaminophen toxicities in small animals are due to intentional administration by the owner in an attempt to treat pain or malaise in their pets.[5,8]

Acetaminophen is metabolized in the liver via one of three pathways: (1) it is conjugated to a sulfate compound by a phenol sulfotransferase, (2) it is conjugated to a glucuronide compound by a uridine diphosphate-glucuronosyl transferase, or (3) it can be transformed and oxidized by the cyto-chrome P-450 system which converts it to the reactive intermediate N-acetyl-*P*-benzoquinone-imine (NAPQI).[5] The toxicity of acetaminophen is due to NAPQI.[5,8] The glucuronide and sulfate conjugations are nontoxic and are excreted in the bile and urine in most species other than the cat.[5,8] Glutathione reacts with NAPQI to form a nonreactive molecule, mercapturic acid, which is excreted in the urine.[8] Low doses of acetaminophen are readily metabolized to nontoxic products, but higher doses can overwhelm the sulfate and glucuronide conjugate systems of the liver and deplete glutathione stores.[5] Ultimately, the toxic metabolite NAPQI builds up and unmetabolized acetaminophen accumulates.[5] Thus the half-life of acetaminophen becomes longer with higher dosages.[5]

Cats are very limited in the degree of glucuronide conjuga-tion that they can perform, because they lack a specific form of the enzyme glucuronyl transferase needed to conjugate acetaminophen.[5,8] Unfortunately, cats also have a somewhat lim-ited sulfate binding capacity, so glutathione stores are depleted and NAPQI accumulates.[5,8] Cats are estimated to have one tenth of the capacity to eliminate acetaminophen compared to

dogs.[5] NAPQI oxidizes hepatic proteins, resulting in hepatocellular damage. Once glutathione stores are depleted in erythrocytes, NAPQI causes intracellular oxidative damage, converting hemoglobin to metHb and oxidizing SH groups on hemoglobin, leading to the formation of HzBs.[5] Methemoglobinemia becomes overt when metHb reductase and necessary reducing equivalents (i.e., NADH) become depleted in erythrocytes. Following the acute episode of metHb production, HzBs begin to form and aggregate into larger structures, eventually causing enough changes in the erythrocyte to trigger hemolysis.[5] Although cats tend to develop metHb and HzB anemia and dogs undergo a significant hepatic insult with acetaminophen toxicity, there is much individual variation, and many animals have evidence of both.[5] The prognosis for acetaminophen toxicity is guarded, with evidence in both veterinary and human literature that time from ingestion to treatment is the most important factor in determining morbidity and survival.[5,8]

88.4.2 Topical Benzocaine

Benzocaine sprays for laryngeal spasm in cats and over-the-counter creams for pruritus in dogs and cats have been associated with methemoglobinemia.[2,3,6] An experimental study evaluating a 2-second spray of aerosolized 14% benzocaine (approximately 56 mg) demonstrated an increase in metHb levels in cats and dogs, with cats more strongly affected than dogs.[6] However, dogs did develop a more significant reaction if they received the benzocaine intravenously.[6] Metabolites of benzocaine are likely responsible for oxidative damage to hemoglobin.[6] The effects of HzBs associated with benzocaine toxicity are generally mild and rarely associated with hemolysis.[2]

88.4.3 Skunk Musk

There is one case report of methemoglobinemia and HzB hemolytic anemia in a dog following exposure to skunk musk.[10] The toxic substances in skunk musk are thought to be thiols, which can react with oxyhemoglobin to form metHb, a thiyl radical, and hydrogen peroxide.[10]

88.4.4 Nitrites and Nitrates

Unlike most substances that cause methemoglobinemia, nitrites and nitrates are not documented to cause HzB production.[3] Exposure to these substances could occur in small animals that receive vasodilatory drugs that release nitric oxide, drugs such as nitroglycerin and sodium nitroprusside.[13] Nitric oxide is decomposed in vivo by interacting with oxyhemoglobin to form metHb and nitrate.[13,14] The metHb is reduced by metHb reductase in red blood cells, but some evidence indicates that nitric oxide decreases metHb reductase activity.[14] Nitric oxide also interacts with oxygen to form nitrogen dioxide (NO_2), which dissolves in solution and yields nitrite and nitrate.[13,14] Nitrite can also convert oxyhemoglobin to metHb.[14] Although significant methemoglobinemia has not been reported in the veterinary literature associated with nitroglycerin or nitroprusside, it is a potential complication of these agents and may contribute to the morbidity of patients requiring therapy with these drugs. Toxicity should be considered in animals receiving these drugs and developing an unexplained hyperlactatemia.

88.4.5 Methemoglobin Reductase Deficiency

MetHb reductase deficiency is a rare congenital abnormality.[15] Affected animals cannot efficiently reduce metHb (see Box 88-1) and therefore have elevated blood levels (18% to 41%), mild to moderate cyanosis of the mucous membranes (present in 100% of cases), and may suffer from exercise intolerance (present in <50% of cases).[15] A definitive diagnosis is obtained by measuring erythrocyte metHb reductase enzyme activity at a research laboratory.[2,15] The defect has been documented in one domestic shorthaired cat and several breeds of dogs, including the Chihuahua, Borzoi, English Setter, Terrier mix, Cockapoo, Poodle, Corgi, Pomeranian, and toy Eskimo dogs.[2]

In humans this disorder is an inherited, autosomal recessive defect, but familial studies in dogs have not been done. This condition is typically fairly benign, rarely requires treatment, and affected dogs have a normal life span.[2,15] Indications for treatment include clinical signs of methemoglobinemia such as lethargy, tachycardia, or tachypnea, and potentially in preparation for general anesthesia.[4]

88.5 DIAGNOSIS

88.5.1 Clinical Signs

The clinical presentation of methemoglobinemia is consistent with decreased oxygen carrying capacity, cellular hypoxia, and shock.[3] These signs begin with a metHb level of 20% and include tachycardia, tachypnea, dyspnea, lethargy, anorexia, vomiting, weakness, ataxia, stupor, hypothermia, ptyalism, and convulsions in cats, and coma and death if metHb levels reach 80%.[5,8,15] Chocolate-brown mucous membranes and cyanosis are common findings, with cyanosis appearing at metHb levels of 12% to 14% or more (Color Plate 88-1).[15] Cats can also develop head, neck, and limb edema associated with acetaminophen toxicity,[5,8] and facial edema has been reported with repeated administration or with propofol.[9]

88.5.2 Determining Methemoglobin Presence and Levels

Methemoglobinemia is apparent on blood sampling because the blood has a chocolate-brown discoloration. A simple qualification test can be performed by placing a drop of venous blood from the patient on a white piece of paper next to a drop of control blood. After exposure to oxygen in the air, the control blood will have a distinctly red appearance, but blood with more than 10% metHb will remain dark with a brown discoloration.[2,15] Similarly, one can observe blood in a tube containing ethylenediaminetetraacetic acid (EDTA).[15] If the blood contains deoxyhemoglobin as a result of cardiac or respiratory disease, it will turn red when exposed to room air for 15 minutes. However, if the blood contains elevated levels of metHb, it will remain dark.

Definitive diagnosis and quantification of metHb levels require direct measurement via a co-oximeter or assay.[15] A co-oximeter is a machine used to measure hemoglobin content, oxygen saturation, percentage of carboxyhemoglobin, and percentage of metHb. An assay for metHb can be performed at some veterinary and human laboratories and involves spectrophotometrically quantifying the change in absorbance at 630 nm before and after the addition of cyanide to the sample.[16] The cyanide converts metHb to cyanmethemoglobin, which has a different absorbance than metHb.[16]

Examining a peripheral blood smear for HzBs, eccentrocytes, and "ghost" cells can also be helpful when looking for evidence of oxidative damage (see Color Plate 88-2, *A* and *B*). Feline HzBs may appear as pale inclusions within red blood cells or as projections from the surface of the cell (see Color Plate 88-2, *B*).[2,16] Canine HzBs, however, are often small and scattered throughout the cell. These may require stains such as new methylene blue, with which they appear as dark, refractile inclusions, or a reticulocyte stain with which they appear as light blue inclusions.[2] "Ghost" cells contain HzBs seen as red inclusions within an erythrocyte membrane or "ghost."[2] Eccentrocytes are cells with hemoglobin concentrated at one side of the cell and are formed by the adhesion of the erythrocyte membrane from opposing sides of the cell.[2,4]

88.6 TREATMENT

Treatment of animals with methemoglobinemia initially involves recognition, careful history acquisition, and elimination of the source of oxidative damage, if possible. Although oxygen therapy will increase the amount of dissolved oxygen in the blood, the hemoglobin capable of carrying oxygen is usually maximally saturated, and oxygen therefore not sufficient as a sole therapy. Oxygen administration, however, is often the first line of therapy while a full assessment and treatment plan are established.[2,5] Therapy for methemoglobinemia often involves diuresis or medications to increase the rate of elimination or decrease the production of toxic metabolites.[5] Induction of vomiting followed by the administration of activated charcoal should be considered if the animal has a history of recently ingesting a toxic substance and is not yet clinically ill (see Chapter 77, Approach to Poisoning and Drug Overdose).[5,8] Supportive care is also important to correct volume status, hydration, and electrolyte or acid-base disturbances.[5]

88.6.1 N-Acetylcysteine

N-Acetylcysteine (NAC) is considered the treatment of choice for the treatment of acetaminophen toxicity.[17] NAC augments the endogenous glutathione stores as it is hydrolyzed to cysteine (one of the components of glutathione).[5,8,17] Glutathione therapy is of minimal value to these patients, because it is not capable of penetrating cells and must be synthesized within the cell. NAC also interacts directly with the reactive metabolite of acetaminophen, NAPQI, to form a nontoxic conjugate and increases the fraction of acetaminophen excreted as the sulfate conjugate.[5,17] The half-life of acetaminophen is halved in cats treated with NAC.[17] NAC is most effective if administered within 12 hours of ingestion of acetaminophen, but is still recommended up to 36 to 80 hours after ingestion.[5,17]

The recommended regimen is an initial dose of 140 mg/kg IV (280 mg/kg in severe toxicosis) followed by 70 mg/kg q6h for seven additional treatments.[5,8] NAC typically causes nausea and vomiting when given orally, hypotension and bronchospasm if given rapidly intravenously, and phlebitis if it leaks perivascularly.[17] Because of these adverse effects, the recommended route of administration in acetaminophen toxicity is a slow intravenous infusion of a 5% solution (10% or 20% NAC solution diluted with 5% dextrose or physiologic saline) over 30 to 60 minutes through a 0.2-μm Millipore filter (because the product is not formulated for intravenous use).[8,17]

88.6.2 Methylene Blue

Methylene blue is a management strategy for the treatment of methemoglobinemia that increases the rate of reduction of metHb through utilization of another reducing system within the erythrocyte, NADPH dehydrogenase.[3] Methylene blue is administered as a 1% solution intravenously over several minutes at a dosage of 1 mg/kg once.[2] Improvement in clinical parameters should be noted within 30 minutes of administration.[2] Methylene blue, however, causes oxidative damage in red blood cells, particularly in cats, and can potentiate a HzB anemia caused by the original oxidative insult.[2,3] A delayed reaction may occur (days after drug administration); therefore the hematocrit should be monitored closely for 3 to 4 days following administration.[2] One study comparing the efficacy of methylene blue with that of NAC for the treatment of acetaminophen toxicity in cats demonstrated minimal effect on the half-life of metHb with methylene blue therapy and possible attenuation of the beneficial effects of NAC on the half-life of acetaminophen in male cats when both drugs were given.[18]

88.6.3 Adjunctive Treatments

Multiple other treatment modalities have been used to treat methemoglobinemia, HzB anemia, and acetaminophen toxicity. These include ascorbic acid (vitamin C),[2,5,8] cimetidine,[5,8] S-adenosylmethionine (SAMe),[19] bioflavonoids,[3,20] and blood transfusions.[5,11] Ascorbic acid is used at a dosage of 30 mg/kg IV q6h as an antioxidant and can augment metHb conversion to hemoglobin through nonenzymatic reduction.[5,8] Cimetidine, a histamine-2 receptor antagonist, is theoretically useful in cases of acetaminophen toxicity, because it inhibits the P-450 oxidation system in the liver, limiting the production of the toxic metabolite.[5,8] Studies evaluating the efficacy of cimetidine-induced alterations of acetaminophen metabolism in humans, however, have not been able to demonstrate consistent benefits.[8] It can be used as adjunctive therapy in acetaminophen toxicity, because it works at a site additional to that of other therapies.[8] The recommended dosage is 5 mg/kg IV q8h.[5] SAMe is an essential metabolite that is vital to hepatocytes and has been reported to be hepatoprotective, have antioxidant properties, and to decrease the osmotic fragility of erythrocytes.[19,21] An experimental, prospective study evaluating the effects of SAMe for the treatment of acetaminophen intoxication in cats revealed no apparent effect on metHb formation, but some efficacy in decreasing the number of HzBs formed and the degree of anemia.[19]

Bioflavonoids are antioxidants that work by increasing the activity of the NADPH reductase system, an alternative physiologic metHb system that uses flavins as substrates for reduction.[3] A prospective, experimental trial evaluating cats that were subjected to acetaminophen toxicity demonstrated a significantly decreased number of HzBs formed in the cats that received bioflavonoids.[20] As with the therapeutic effects of SAMe, however, there was no significant difference in the amount of metHb produced.[20] Blood transfusion may be necessary in patients with severe hemolytic anemia secondary to HzB production.[5]

88.7 SUGGESTED FURTHER READING*

LE Bahri, N Lariviere: Pharm profile: N-acetylcysteine. *Compend Contin Educ Pract Vet*. **25**, 2003, 276, *A concise review of the mechanism of action, indications, administration, and complications associated with NAC*.

JW Harvey: Methemoglobinemia and Heinz body hemolytic anemia. In J Bonagura (Ed.): *Kirk's current veterinary therapy XIII: small animal practice*. ed 13, 2000, Saunders, Philadelphia, *An overview of causes, clinical signs, and treatment of methemoglobinemia and HzBs anemia in small animals*. 377 378

WK Rumbeiha, L Yu-Shange, W Oehme, et al.: Comparison of N-acetylcysteine and methylene blue, alone or in combination, for treatment of acetaminophen toxicosis in cats. *Am J Vet Res*. **56**, 1995, 1529, *A controlled, prospective trial that compares the beneficial effects of methylene blue in acetaminophen toxicity in cats*.

NS Taylor, N Dhupa: Acetaminophen toxicity in cats and dogs. *Compend Contin Educ Pract Vet*. **22**, 2000, 160, *A complete discussion on the pathophysiology, clinical signs, and treatment of acetaminophen toxicity in dogs and cats*.

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* See the CD-ROM for a complete list of references.

89 Chapter 89 Cyclic Antidepressant Drug Overdose

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89.1 KEY POINTS

- Cyclic antidepressant toxicities cause anticholinergic, cardiovascular, and central nervous system effects. Cardiovascular effects tend to be the most life threatening.
- These drugs are commonly prescribed for the treatment of depression in people and a variety of disorders in dogs and cats, including inappropriate urination or incontinence, neuropathic pain, urinary tract obstruction, and separation anxiety.
- Cyclic antidepressants are absorbed rapidly and have variable half-lives in dogs and cats, ranging from 2 to 32 hours. Therefore clinical signs of intoxication generally occur quickly after ingestion and can persist for several days.
- Treatment includes gastrointestinal decontamination, aggressive management of acidosis and arrhythmias, and control of seizures.
- Prognosis for patients who remain asymptomatic or mildly affected for the first 6 to 12 hours after ingestion is good, but for patients with severe arrhythmias, hypotension, or refractory seizures the prognosis is guarded.

89.2 INTRODUCTION

The use of antidepressants in small animals for a number of disorders including inappropriate urination or incontinence, neuropathic pain, urinary tract obstruction, and separation anxiety is growing, and thus the incidence of accidental overdose has also increased. Between 1998 and 2000, the American Society for the Prevention of Cruelty to Animals' Animal Poison Control Center received more than 1075 reports of accidental antidepressant drug ingestion.[1]

One of the most common types of antidepressants prescribed for companion animals is the cyclic antidepressant (CA), which consists of multiple-ring aromatic nuclei and an aliphatic aminopropyl side chain. CAs can be divided into subclasses based on the number of rings. Box 89-1 shows a list of CAs grouped by the number of rings. The most common of these drugs used in veterinary medicine are the tricyclic antidepressants (TCAs) amitriptyline (Elavil, AstraZeneca), imipramine (Tofranil, Novartis), and clomipramine (Clomicalm, Novartis). Although newer antidepressants that have a wider margin of safety and are less likely to cause severe side effects in people are available, such as the selective serotonin reuptake inhibitors and reversible monoamine oxidase-A inhibitors, CAs are still widely prescribed in people. A recent study of antidepressant poisonings in people showed that 43% were due to CAs,[2] and the most recent survey of toxicities reported to American poison control centers showed that antidepressants were the second most common class of drug responsible for fatalities, with amitriptyline being the most common agent involved.[3] These data suggest that companion animals are at risk of exposure from both veterinary and human products.

89.2.1 Box 89-1 Cyclic Antidepressants Listed by the Number of Aromatic Rings

89.2.1.1 Monocyclic Antidepressants

Bupropion

89.2.1.2 Dicyclic Antidepressants

Amoxapine (dibenzoxazepine class)

89.2.1.3 Tricyclic Antidepressants

Amitriptyline (Elavil)

Doxepin (Sinequan)

Imipramine (Tofranil)

Clomipramine (Clomicalm: dogs, Anafranil: humans)

Trimipramine

Desipramine

Nortriptyline

Protriptyline

89.2.1.4 Tetracyclic Antidepressants

Maprotiline

The CAs are thought to exert their therapeutic effects in the central nervous system via inhibition of presynaptic amine pumps responsible for reuptake of norepinephrine and serotonin, resulting in an increased concentration of these neurotransmitters in the synaptic cleft. Organic depression is thought to be mediated, at least in part, by deficits in the concentrations of these neurotransmitters. In addition to these therapeutic effects, CAs also cause sedation, have both peripheral and central anticholinergic effects (via blocking of muscarinic receptors), cause α_1-adrenergic blockade, and are antagonists at histamine receptors (H_1 and H_2).[4]

Table 89-1 Therapeutic Doses, Toxic Doses, and Pharmacokinetics of Common Tricyclic Antidepressants

Drug	Trade Name(s)	Therapeutic Dose	Toxic Dose	Peak Serum Level	Half-life
Amitriptyline	Elavil	0.25 to 4.4 mg/kg PO q12h	Unknown	2 to 12 hr[15]	6 to 8 hr[15] (dog) Unknown (cat)
Clomipramine	Clomicalm (dogs), Anafranil (humans)	0.5 to 4 mg/kg PO q12h	50 to 100 mg/kg	1 hr[16] (dog)	5 hr[16] (dog)
Imipramine	Tofranil	0.5 to 4.4 mg/kg PO q12h	Unknown	1 to 2 hr[15] (human)	8 to 16 hr[15] (human)

89.3 PHARMACOKINETICS

The pharmacokinetic profiles of the CAs are highly variable, both among drugs and among individuals. However, there are some common characteristics. All of the drugs are absorbed rapidly from the gastrointestinal (GI) tract, as well as from parenteral injection. Peak plasma concentrations occur within 1 to 12 hours. Plasma half-life is variable and depends on the specific drug (Table 89-1), but ranges from 2 to 32 hours for the most common veterinary CAs. They are highly lipophilic, cross the blood-brain barrier, and are extensively protein bound. They cross the placenta and are present in the milk in comparable or higher concentrations than in the serum. CAs are metabolized in the liver, and some of the metabolites are biologically active. Most of the drugs undergo enterohepatic recirculation, with excretion occurring predominantly via the urine, and to a lesser extent in the feces.[1]

89.4 CLINICAL SIGNS

Clinical signs of CA overdose are due to both central and peripheral effects, and can become apparent within 30 minutes of ingestion because of rapid absorption. Progression can occur quickly, with death occurring within 1 to 2 hours without intervention.[5] The main clinical signs of CA overdose are due to CNS disturbances from anticholinergic effects and elevations of norepinephrine and serotonin concentrations, and cardiovascular disturbances from peripheral anticholinergic effects, α-adrenergic blockade, and blocking of sodium channels in cardiac tissue.

89.4.1 Anticholinergic Effects

Clinical manifestations of the central and peripheral anticholinergic effects of CA toxicity include mydriasis, fever, dry mucous membranes, ileus, urinary retention, lethargy, tachycardia, disorientation and coma (see Chapter 90, Anticholinergic Poisonings).

89.4.2 Cardiovascular Effects

The most common cardiovascular effect of CA toxicity is sinus tachycardia, which can be profound. Life-threatening ventricular tachycardias and ventricular fibrillation can ultimately result. QRS waves, QT segments, and PR intervals become prolonged as a result of the direct local anesthetic effects of CAs, which block sodium channels in cardiac myocyte membranes. In experimentally intoxicated dogs, QRS intervals longer than 0.11 second were associated with ventricular tachyarrhythmias.[6] In human medicine, it has been reported in multiple studies that death from CA overdose is most commonly due to cardiac toxicity and usually occurs within the first 24 hours after admission.[7]

Other cardiovascular effects can include vasodilation and systemic hypotension secondary to peripheral α_1-adrenergic blockade and myocardial depression, right bundle branch block due to the effect on fast sodium channels in Purkinje and pacemaker cells, and atrioventricular block.

89.4.3 Seizures

Seizures occur because of the increased concentrations of serotonin and norepinephrine within the brain. In some patients they are short lived and mild, but in others they can be protracted and refractory to treatment. In humans, an association between widened QRS complexes (greater than 0.1 second) and seizures has been reported.[8] In addition, elevated concentrations of serotonin can lead to serotonin syndrome, which is characterized by tremors, seizures, ataxia, vomiting, diarrhea, abdominal pain, hyperthermia, depression or excitation, and hyperesthesia (see Chapter 91, Serotonin Syndrome).

89.5 TREATMENT

Treatment of CA toxicity should include basic GI decontamination procedures, treatment of cardiac arrhythmias, support of systemic blood pressure, and treatment of CNS signs. Supportive care and monitoring are targeted at identifying and treating life-threatening disturbances.

89.5.1 Emesis Induction

If ingestion has occurred within 1 hour and the patient is neurologically and cardiovascularly stable, gastric decontamination is indicated. Emesis induction is controversial because of the possibility of unexpected seizures or acute neurologic deterioration and the accompanying risk of aspiration. In canine patients without any signs, apomorphine given intravenously or into the conjunctival sac, or hydrogen peroxide given orally may be used to induce emesis. If the patient is showing signs of intoxication, emesis induction is not recommended because of the high risk of aspiration and the limited utility of this procedure when significant absorption of the toxin has already occurred. Anesthesia, intubation with a cuffed endotracheal tube, and gastric lavage are suggested in these patients.

89.5.2 Activated Charcoal

An initial dose of activated charcoal (1 to 2 g/kg PO) is recommended in all cases. Although these drugs undergo enterohepatic recirculation, the use of repeated doses of activated charcoal is controversial because of the risk of GI obstruction secondary to the profound ileus that can develop as a result of the CAs anticholinergic effects.

Repeated doses of activated charcoal (0.5 to 1 g/kg PO q4-6h for 24 to 48 hours) can be administered, but frequent assessment of GI motility and monitoring for signs of obstruction are required.

89.5.3 Cathartics

A single dose of a saline or osmotic cathartic may be administered to hasten GI decontamination. However, magnesium salt cathartics are contraindicated because of toxicity that may be caused by increased magnesium absorption in patients with decreased GI motility.

89.5.4 Diuresis

Because CAs primarily undergo renal excretion, fluid diuresis is indicated to hasten clearance of these toxins. In patients without evidence of heart failure, intravenous crystalloids should be administered at 2 to 3 times the normal maintenance rates. Respiratory rate and effort should be monitored closely, and the chest should be auscultated frequently for evidence of pulmonary edema.

89.5.5 Sodium Bicarbonate

Alkalinization is considered the standard of care in human medicine for all patients with widening of the QRS interval (greater than 0.1 second) due to CA intoxication. This measurement is a reliable predictor of the severity of intoxication.[5] Metabolic acidosis can result from cardiac arrhythmias and from seizures, causing increased dissociation of toxin from blood protein and worsening of the systemic toxic effects. Sodium bicarbonate, given at a dosage of 2 to 3 mEq/kg slowly intravenously (over approximately 2 minutes), has been shown in experimentally intoxicated dogs to improve survival. In vitro studies suggest that both the change in pH and the increase in extracellular sodium concentration have beneficial effects on Purkinje fibers.[6] Recommendations are to administer repeated doses until the QRS complex width is less than 0.1 second or pH is higher than 7.55.[9] Because of the risk of severe iatrogenic metabolic alkalosis or paradoxical cerebral acidosis in hypercapnic animals, sodium bicarbonate therapy should not be instituted if blood gas analysis is not available.

89.5.6 Blood Pressure Support

After an initial period of hypertension due to increased norepinephrine levels, some patients with CA toxicity subsequently develop hypotension. Intravenous crystalloids should be administered to support blood pressure. Sodium bicarbonate may also be helpful in managing the cardiac disturbances leading to hypotension. Patients who exhibit refractory hypotension should be treated with vasopressors, inotropic agents, or both (see Chapter 176, Vasoactive Catecholamines). Dopamine generally is considered a poor choice, because CAs inhibit dopamine-induced catecholamine release, but study results are conflicting. Recommendations in human medicine suggest norepinephrine as a first-line vasopressor, and dobutamine in patients with evidence of myocardial failure.[10]

89.5.7 Antiarrhythmic Agents

Patients that develop ventricular arrhythmias and do not respond to sodium bicarbonate should be given lidocaine (2 mg/kg boluses slowly intravenously to effect). Lidocaine is a class IB antiarrhythmic agent that binds to inactive fast sodium channels and slows repolarization but has little to no effect on the QRS interval. Class IA antiarrhythmic drugs (e.g., procainamide) should not be administered, because they are potent sodium channel blockers that further widen the QRS complex, and thus may potentiate the detrimental sodium channel blocking effects of the CAs.[9]

89.5.8 Anticonvulsants

Seizures should be managed aggressively to combat life-threatening hyperthermia, acidosis, and rhabdomyolysis. Intravenous (bolus) or rectal diazepam (0.5 mg/kg) should be administered initially to control seizures. Further treatment may not be necessary for patients with transient seizures. However, patients refractory to multiple doses of benzodiazepines should be anesthetized with propofol (1 to 2 mg/kg bolus intravenously, followed by a constant rate infusion of 0.1 to 0.4 mg/kg/min) to stop the seizures (see Chapter 186, Anticonvulsants). Ventilation should be monitored carefully using arterial or venous blood gas measurements, and patients that persistently hypoventilate should be mechanically ventilated (see Chapter 213, Basic Mechanical Ventilation). Once initial seizures are controlled in refractory patients, a loading dose of phenobarbital (16 mg/kg IV over 24 hours, divided into 4 to 6 doses), followed by maintenance phenobarbital therapy (2 mg/kg IV or PO q12h), should be instituted.[7]

89.5.9 Acetylcholinesterase Inhibitors

Physostigmine is an anticholinesterase drug and was historically recommended as treatment for the anticholinergic effects of CA toxicity. However, several studies have shown significant complications from this drug, including bradycardia, seizures, vomiting, cardiac conduction disturbances, cardiac arrest, and death.[11] Although its use in CA intoxications is still controversial, recommendations in human medicine support use of this drug if residual antimuscarinic effects are present after prolonged observation. For more information on this topic, the reader is referred to the very thorough review of the relevant literature by Suchard.[12]

89.5.10 Serotonin Antagonists

Because CAs inhibit serotonin reuptake, treatment with serotonin antagonists (e.g., cyproheptadine) should be considered in patients exhibiting clinical signs of serotonin syndrome.[13] Cyproheptadine can be administered rectally or orally at a dosage of 1.1 mg/kg q1-4h until the signs resolve.[14] If there is no improvement after 2 to 3 doses, additional doses should not be administered because of the potential for anticholinergic toxicity (see Chapters 90 and 91, Anticholinergic Poisonings and Serotonin Syndrome, respectively).

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89.6 PROGNOSIS

Data on prognosis in veterinary patients are limited. Patients that are asymptomatic initially and remain so for 6 to 12 hours are unlikely to have significant signs of toxicity. In these patients, hospitalization for monitoring and continuous or repeated electrocardiographic recordings should be recommended. Patients who have severe anticholinergic or neurologic signs will require intensive supportive care and monitoring for several days, and carry a more guarded prognosis.

89.7 SUGGESTED FURTHER READING*

SM Gwaltney-Brant, WK Rumbeiha: Newer antidotal therapies. *Vet Clin North Am Small Anim Pract.* **32**, 2002, 323, *A good review of the use of cyproheptadine to treat serotonin syndrome in dogs.*

WA Watson, TL Litovitz, GC Rodgers, Jr., et al.: 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*. **23**, 2005, 589, *Annual report of poison control centers showing that antidepressants were among the most common groups of agents causing fatalities, with CAs being the most common type of antidepressant involved in toxicoses*.

T Wismer: Antidepressant drug overdoses in dogs. *Vet Med*. **95**, 2000, 520, *A good, brief discussion of the pharmacology, incidence, treatment, and prognosis of antidepressant drug overdoses in dogs using data from the American Society for the Prevention of Cruelty to Animals' Animal Poison Control Center*.

[*] See the CD-ROM for a complete list of references.

90 Chapter 90 Anticholinergic Poisonings

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90.1 KEY POINTS

- The main symptoms of anticholinergic toxicity are due to blockade of peripheral muscarinic receptors and include bilateral unresponsive mydriasis, dry mucous membranes, decreased borborygmi due to decreased gastrointestinal (GI) motility, sinus tachycardia or supraventricular tachyarrhythmias, urinary retention, and hyperthermia.
- Many of these agents cross the blood-brain barrier and can cause disorientation, ataxia, agitation, and seizures.
- A wide variety of drugs, including antihistamines, antidepressants, and phenothiazines, can cause anticholinergic symptoms.
- Management involves GI decontamination, symptomatic therapy and, in selected cases, acetylcholinesterase inhibitors.
- Prognosis depends on severity of exposure and symptoms, with fair to good prognoses for asymptomatic or mildly affected patients, and guarded to poor prognoses for animals with central nervous system symptoms.

90.2 INTRODUCTION

Neurotransmission within the autonomic nervous system may be divided functionally into the sympathetic and parasympathetic systems, or chemically into the adrenergic and cholinergic systems. The cholinergic division consists of all synapses at which acetylcholine is the chemical mediator released. The cholinergic portion of the autonomic nervous system consists of: (1) all preganglionic neurons in the sympathetic and parasympathetic systems, (2) all postganglionic neurons of the parasympathetic system, (3) postganglionic sympathetic neurons that innervate sweat, salivary, lacrimal, and nasopharyngeal glands, and (4) postganglionic sympathetic neurons that innervate skeletal muscle and blood vessels and induce vasodilation when stimulated. The responses of various effector organs to cholinergic stimulation are shown in Table 90-1. Generally, cholinergic neurons can be considered those responsible for an anabolic or vegetative state, stimulating digestion, decreasing cardiac work, and relaxing vascular smooth muscle.

Postsynaptic cholinergic receptors can be further subdivided into two pharmacologic classes, muscarinic and nicotinic. Muscarinic receptors, named because of the selective action of muscarine, an alkaloid found in toadstools, are postsynaptic receptors found within the central nervous system (CNS) and on smooth muscle and glands, but not within autonomic ganglia. Muscarinic receptors are further divided into five subtypes (M_1 to M_5), each located within a specific part of the body, and each having its effect via a second messenger G-protein system.

Nicotinic receptors are found within the autonomic ganglia as well as on skeletal muscle and within the CNS. They were named because they selectively respond to the application of nicotine, which causes opening of an ion channel that allows passage of sodium, calcium, potassium, and other small cations. Because these receptors do not use second messenger systems, responses to stimulation are rapid in onset and short in duration, and they are generally excitatory in nature. Each receptor is made up of five subunits that have varying binding affinities for cholinergic agonists and antagonists, and the subunits vary depending on the tissue in which the receptor is located.

Many plants contain anticholinergic compounds, as do numerous drugs. Box 90-1 contains a listing of plants and drugs that can cause anticholinergic toxicity.[1] The drugs are further divided into those in which anticholinergic activity causes the primary toxic effect and those in which anticholinergic effects occur but other toxic effects are more likely to be life threatening. Although exposure to toxic plants with anticholinergic effects is less common in small animals than in large animals, case reports of natural exposures exist.[2] The classes of drugs most commonly associated with anticholinergic toxicity in small animals include antihistamines (e.g., diphenhydramine) and tricyclic antidepressants (e.g., amitriptyline, clomipramine). In addition, it is important to assess the possibility of exposure to human medications, such as anti-Parkinsonian drugs and antinausea medications (e.g., promethazine).

Table 90-1 Responses of Effector Organs to Cholinergic Stimulation

Effector Organs	Cholinergic Response
Ophthalmic	
Iris sphincter	Contraction (miosis)
Ciliary muscle	Contraction (near vision)
Cardiac	
SA node	Decrease heart rate
Atria and ventricles	Decrease contractility
AV node and His-Purkinje system	Slow conduction
Vascular	
Coronary, skin, mucosa, skeletal muscle, cerebral, pulmonary, salivary arterioles	Dilation
Systemic veins	No effect
Pulmonary	
Bronchioles	Constriction
Bronchial glands	Secretion
Gastrointestinal	
Motility and tone	Increase
Mucous glands	Secretion
Pyloric sphincter	Increase tone
Intestinal sphincters	Decrease tone
Gall bladder and ducts	Contraction
Urinary	
Detrusor	Contraction
Trigone and sphincter	Relaxation
Ureter motility and tone	Increase
Endocrine / Glandular	
Adrenal medulla	Secretion of epinephrine and norepinephrine
Pancreatic acini and islet cells	Increase secretion
Salivary, lacrimal and nasopharyngeal glands	Increase secretion

Modified from Brunton LL: *Goodman & Gilman's the pharmacological basis of therapeutics*, ed 11, New York, 2005, McGraw-Hill.

AV, Atrioventricular; *SA,* sinoatrial.

90.3 CLINICAL SIGNS

Clinical signs of anticholinergic toxicity are associated most commonly with muscarinic effects. Blockade of peripheral muscarinic receptors causes bilateral unresponsive mydriasis, dry mucous membranes, decreased borborygmi due to decreased gastrointestinal (GI) motility, sinus tachycardia or supraventricular tachyarrhythmias, and urinary retention. In humans, hyperthermia is also commonly reported because of the inability to sweat. Since small animals do not rely on evaporative cooling from the skin, hyperthermia is uncommon unless severe agitation or seizures occur.

90.3.1 Box 90-1 Anticholinergic Toxins

90.3.1.1 Plants

- Deadly nightshade *(Atropa belladonna)*
- Angel's trumpet *(Brugmansia candida)*
- Night-blooming jessamine *(Cestrum nocturnum)*
- Day-blooming jessamine *(Cestrum diurnum)*
- Trumpet lily *(Datura arborea)*
- Sacred datura *(Datura metaloides)*
- Jimson weed *(Datura stramonium)*
- Henbane *(Hyocyamus niger)*
- Matrimony vine *(Lycium halimifolium)*
- Mandrake *(Mandragora officinarum)*
- Chalice vine, cup-of-gold (*Solandra* spp)

90.3.1.2

Drugs (Primary Anticholinergic Effects)

90.3.1.2.1

Belladonna Alkaloids

Atropine

Scopolamine

Homatropine

Cyclopentolate

Tropicamide

Propantheline

Ipratropium

90.3.1.2.2

Antiparkinsonian agents

Benztropine (Cogentin)

Trihexyphenidyl (Artane)

Procyclidine (Kemadrin)

Biperiden (Akineton)

Ethopropazine (Parsidol)

90.3.1.2.3

H_1 Blockers

Diphenhydramine (Benadryl)

Chlorpheniramine (Chlor-Trimeton)

Clemastine

Brompheniramine (Dimetane)

Cyclizine (Marezine)

Meclizine (Antivert)

Hydroxyzine (Atarax, Vistaril)

Dimenhydrinate (Dramamine)

90.3.1.2.4 Phenothiazines

Promethazine (Phenergan)

90.3.1.3 Drugs (Secondary Anticholinergic Effects*)

90.3.1.3.1 Tricyclic Antidepressants

Amitriptyline (Elavil)

Imipramine (Tofranil)

Clomipramine (Clomicalm)

Cyclobenzaprine (Flexeril)

Carbamazepine (Tegretol)

Doxepin

Amoxapine

Desipramine

Nortriptyline

90.3.1.3.2 Phenothiazines

Acepromazine

Chlorpromazine (Thorazine)

Prochlorperazine (Compazine)

* Drugs that have anticholinergic properties but are likely to exhibit other life-threatening toxic effects before anticholinergic effects.

The development of CNS signs is largely a function of the dose of the toxin ingested and the ability of the toxin to penetrate the blood-brain barrier. The most common clinical signs include disorientation, agitation, ataxia, and hyperactivity. With severe intoxications, seizures, coma, respiratory failure, and cardiovascular collapse may be seen.[3]

Clinical signs are highly variable in humans with anticholinergic intoxications, and many patients exhibit only a few of the “classic” anticholinergic signs, most commonly dry mucous membranes and sinus tachycardia.[4] There have been no similar descriptive studies of the most common clinical signs associated with anticholinergic toxicity in small animals.

90.4 TREATMENT

Treatment of anticholinergic toxicity consists of GI decontamination and supportive care (see Chapter 77, Approach to Poisoning and Drug Overdose). The use of acetylcholinesterase inhibitors to increase the effective concentration of acetylcholine in the synaptic cleft is controversial, but it should be considered in patients with severe agitation or severe tachyarrhythmias.

90.4.1 Gastrointestinal Decontamination

In the case of recent oral ingestion (within 1 to 2 hours) in asymptomatic animals, emesis induction is indicated. In patients showing neurologic signs or other clinical anticholinergic manifestations, induction of emesis is contraindicated because of the risk of aspiration. In these patients, anesthesia, intubation with a cuffed endotracheal tube, and gastric lavage should be performed. Activated charcoal should be administered (1 to 2 g/kg) with a saline or osmotic cathartic. Some of these agents undergo enterohepatic recirculation (e.g., cyclic antidepressants), but others do not (e.g., atropine, antihistamines). For those that do undergo enterohepatic recirculation, the use of repeated doses of activated charcoal is controversial because of the risk of GI obstruction secondary to anticholinergic-induced ileus. Repeated doses of activated charcoal (0.5 to 1 g/kg) q4-6h for 24 to 48 hours can be administered, but frequent evaluation of GI motility and monitoring for clinical signs of GI obstruction are required.

90.4.2 Anticonvulsants

Seizures should be treated aggressively. Benzodiazepines are the first line-therapy (diazepam or midazolam, 0.5 mg/kg IV or per rectum to effect). Patients refractory to multiple doses of benzodiazepines should be anesthetized with propofol (2 to 6 mg/kg bolus, followed by a constant rate infusion of 0.05 to 0.4 mg/kg/min) to stop seizures (see Chapter 98 and Chapter 186, Seizures and Status Epilepticus and Anticonvulsants, respectively). Ventilation should be monitored carefully using arterial or venous blood gas measurements, and patients with persistent hypercapnia should be mechanically ventilated (see Chapter 213, Basic Mechanical Ventilation). Once initial seizures are controlled in refractory patients, a loading dose of phenobarbital (16 mg/kg IV over 24 hours, split into 4 to 6 doses), followed by maintenance phenobarbital therapy (2 mg/kg IV or PO q12h) can be instituted.

90.4.3 Acetylcholinesterase Inhibitors

The use of acetylcholinesterase inhibitors in patients with anticholinergic intoxications is controversial. Agitation and delirium are commonly associated with anticholinergic intoxication. In humans with confirmed anticholinergic toxicity, the acetylcholinesterase inhibitor physostigmine is more effective at controlling these signs than benzodiazepines.[5] Because physostigmine crosses the blood-brain barrier, it can reverse some of the central effects of anticholinergic toxicity. In one case report, neostigmine, a short-acting acetylcholinesterase inhibitor that does not cross the blood-brain barrier, was beneficial in a person with severe ileus secondary to anticholinergic toxicity.[6] Anticholinesterase therapy generally is not recommended in patients with cyclic antidepressant overdose because there have been reports of fatal cardiovascular complications.[7]

Physostigmine has been evaluated experimentally in dogs with anticholinergic intoxication. It reversed CNS signs (seizures, agitation) completely and the peripheral effects (tachycardia, hyperthermia) to a lesser extent at a dosage of 0.02 to 0.07 mg/kg IV.[8] Dogs were given one or more boluses to effect. However, it is imperative that the source of the intoxication be identified definitively as a compound with primarily anticholinergic activity to decrease the risk of iatrogenic cholinergic syndrome. The use of these drugs should be considered only in patients with severe clinical signs, a confirmed diagnosis of anticholinergic poisoning, and in whom cyclic antidepressant intoxication has been ruled out.

90.5 PROGNOSIS

Prognosis is variable depending on the time since ingestion, severity of clinical signs, and other toxic effects of the compound ingested. Patients that are asymptomatic on admission and are treated with early GI decontamination have a good chance of recovery. Those with severe CNS or cardiovascular signs will require hospitalization and intensive supportive care, and carry a more guarded prognosis.

90.6 SUGGESTED FURTHER READING*

K Delaney: Anticholinergics. In JA Marx, RS Hockberger, RM Walls, J Adams (Eds.): *Rosen's emergency medicine: Concepts and clinical practice*. 2005, Mosby, Philadelphia, *A brief discussion of the history, pharmacology, and incidence of anticholinergic intoxications in humans*.

L Murphy: Antihistamine toxicosis. *Vet Med*. **96**, 2001, 752, *A good review of the incidence, prevalence, mechanisms of action, toxic effects, pharmacology, treatment, and prognosis of antihistamine toxicosis in small animals*.

* See the CD-ROM for a complete list of references

91 Chapter 91 Serotonin Syndrome

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91.1 KEY POINTS

- Serotonin (5-hydroxytryptamine [5-HT]) syndrome is a drug-induced condition resulting from excess serotonergic agonism of the central and peripheral nervous system serotonin receptors.
- Serotonin syndrome can result from overdoses of serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressant medications, lithium, dietary supplements, or administration of multiple serotonergic medications.
- Clinical signs reported in companion animals due to accidental ingestion of serotonergic medications include nervous system signs (seizures, depression, tremors, hyperesthesia, ataxia, paresis, disorientation, coma, hyperreflexia, mydriasis, blindness), gastrointestinal tract symptoms (vomiting, diarrhea, abdominal pain, ptyalism, flatulence, bloat), hyperthermia, and death.
- Treatment of symptomatic animals consists primarily of supportive measures, and correction of nervous system and cardiovascular abnormalities, but could also include administration of a 5-HT$_{2A}$ receptor antagonist such as cyproheptadine.

91.2 INTRODUCTION

Over the past 10 years, with mental depression and other psychiatric disorders on the rise, numerous drugs have been developed to manipulate neurotransmitters in the brain. With the increasing use of these antidepressant medications in both humans and animals, it is not surprising that both intentional and accidental ingestions of these medications are also on the rise.

The history of antidepressant medications extends as far back as 1951 with the introduction of the drug isoniazid, and its isopropyl derivative iproniazid, to manage tuberculosis.[1,2] Doctors quickly discovered that patients treated with this drug exhibited signs of elevated mood. This psychotropic effect was found to result from iproniazid's ability to inhibit the enzyme monoamine oxidase, responsible for the breakdown of serotonin, resulting in increased amounts of serotonin in the brain.[1,2] Since that time, evidence has accumulated that the diminished formation of neurotransmitters, serotonin in particular, may be responsible for mental depression.[3] This has led to the development of additional drugs targeted to increase the levels of serotonin in the brain by inhibiting the breakdown of serotonin (monoamine oxidase inhibitors [MAOIs]), increasing serotonin release (amphetamines), and blocking the reuptake of serotonin (selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]).

91.3 DEFINITION

Serotonin syndrome refers to a drug-induced condition resulting from excess serotonergic agonism of the central and peripheral nervous system serotonin receptors. This life-threatening syndrome is characterized by a clinical triad of mental status changes, autonomic instability, and neuromuscular abnormalities.[4] In humans this syndrome can occur following initial administration of an SSRI or more commonly results from the concurrent administration of two serotonergic medications. One of the most common and lethal interactions is the combination of an SSRI with an MAOI.[4,5] In companion animals, this syndrome has been reported only secondary to accidental ingestion but could also occur secondary to therapeutic dosages of serotonergic medications and drug interactions.[6]

91.4 SEROTONIN AND PATHOPHYSIOLOGY OF SEROTONIN SYNDROME

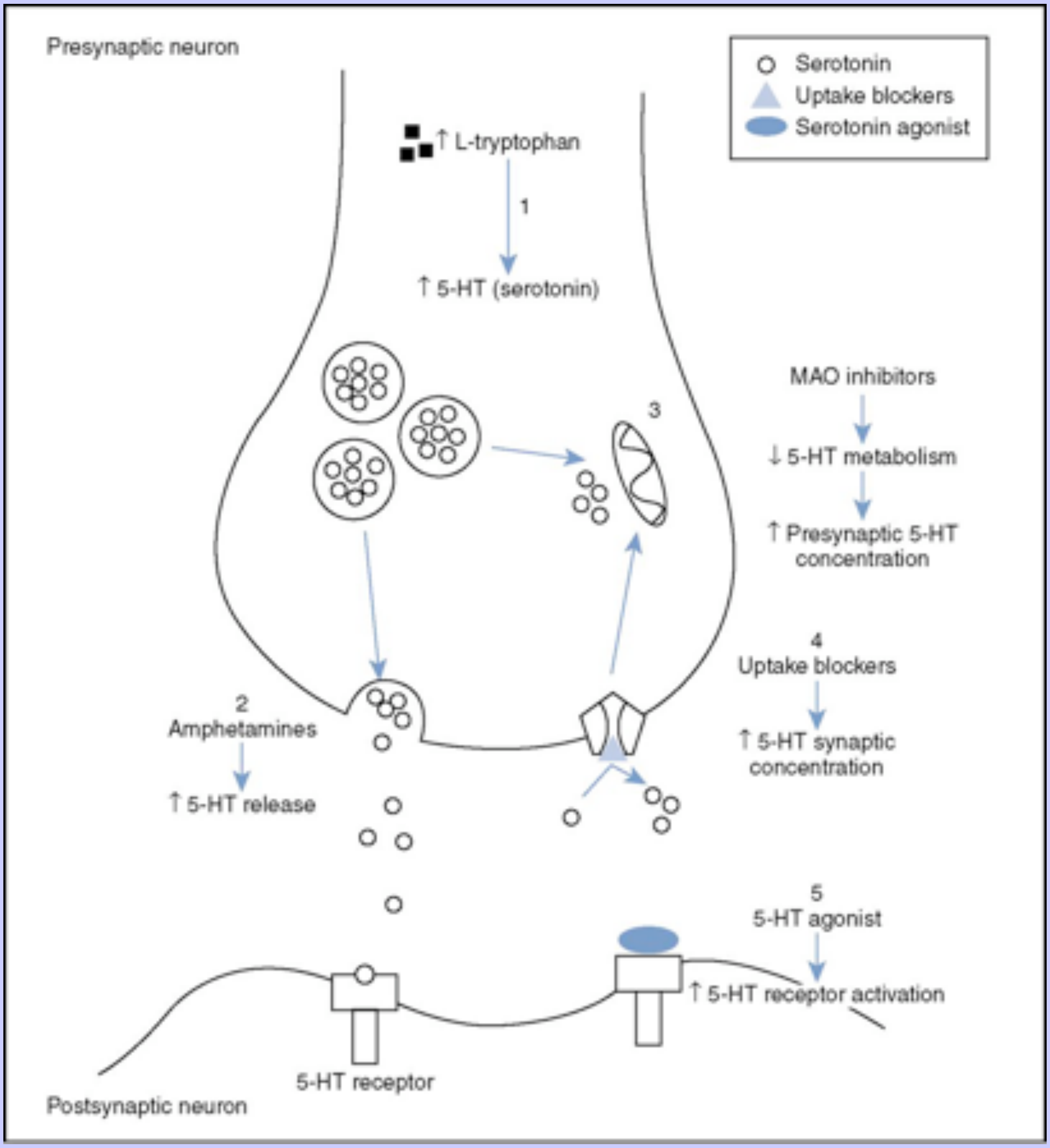
Serotonin exerts its effects in both the peripheral and central nervous systems. Most of the serotonin in the body is synthesized and stored in the enterochromaffin cells and myenteric plexus in the gastrointestinal (GI) tract.[7] Serotonin produced by the enterochromaffin cells in the GI mucosa is scavenged and stored by platelets through an active uptake mechanism. Serotonin is also removed from the circulation by the lungs and either stored there or transferred to platelets.[7]

The effects of serotonin in the peripheral nervous system include vasoconstriction, platelet aggregation, uterine contraction, intestinal peristalsis, and bronchoconstriction.[7,8] Because serotonin cannot cross the blood-brain barrier, it must also be produced in the central nervous system. Most serotonin-producing neurons in the brain are located on the midline raphe nuclei of the lower pons and medulla and project fibers to many areas of the brain and spinal cord.[3] Centrally serotonin exerts influences on mood, aggression, thermoregulation, sleep, vomiting, and pain perception.[3,8]

Serotonin is formed in the body by hydroxylation and decarboxylation of the essential amino acid tryptophan. Increased intake of tryptophan in the diet can increase brain serotonin levels because the enzyme, tryptophan hydroxylase, does not normally reach saturation levels.[7] Serotonin is synthesized in the cytosol in neurons, stored in vesicles at the nerve terminal, and released into the synaptic cleft where it binds to the postsynaptic receptor, mediating neurotransmission. After release, much of the serotonin is recaptured by an active reuptake mechanism and inactivated by monoamine oxidase to form 5-hydroxyindoleacetic acid. This substance is then eliminated in the urine (Figure 91-1).[7]

Seven families of serotonin receptors have been identified (5-HT_1 to 5-HT_7), several of which have multiple members.[4] No single receptor appears to be responsible for serotonin syndrome, although several lines of evidence suggest that the 5-HT_1 and 5-HT_{2A} receptors contribute substantially to the condition.[2,4] Severe serotonin excess can lead to activation of other pathways through the release of noradrenaline, dopamine, and glutamine from the anterior hypothalamus.[9]

Figure 91-1 Mechanisms of serotonin syndrome. *(1)* Increased L-tryptophan will increase serotonin. *(2)* Amphetamines and other drugs increase the release of stored serotonin. *(3)* Inhibition of serotonin metabolism by monoamine oxidase inhibitors *(MAOIs)* will increase presynaptic serotonin concentration. *(4)* Impairment of serotonin transport into presynaptic neurons by uptake blockers (i.e. *SSRI, TCA*) increases synaptic serotonin concentration. *(5)* Direct serotonin agonists can stimulate postsynaptic serotonin receptors.



Drug classes that have been implicated in serotonin syndrome include serotonin precursors, serotonin agonists, serotonin releasers, serotonin reuptake inhibitors, MAOIs, lithium, and herbal medications (Box 91-1).[4]

91.5 CLINICAL SIGNS

In humans, the serotonin syndrome encompasses a wide range of clinical findings ranging from tremor and diarrhea in mild cases to delirium, neuromuscular rigidity, and severe hyperthermia in life-threatening cases. The clinical findings in 2222 serotonergic drug self-poisonings in humans included neuromuscular signs such as hyperreflexia, inducible clonus, myoclonus, ocular clonus, spontaneous clonus, peripheral hypertonicity, and shivering.[10] Autonomic manifestations included tachycardia, mydriasis, diaphoresis, increased bowel sounds, and diarrhea.[10] The mental status abnormalities included agitation and delirium.[10] In severe cases of serotonin syndrome, cardiac arrhythmias, disseminated intravascular coagulation, respiratory compromise, and rhabdomyolysis causing myoglobinuria induced renal failure may occur.[8]

Clinical signs associated with accidental ingestion of antidepressant medication in companion animals mirror those seen in humans with serotonin syndrome. In a retrospective study of 456 companion animal cases of TCA ingestion reported to the Animal Poison Control Center, hyperexcitability and vomiting were the most common initial signs followed by ataxia, lethargy, and muscle tremors.[11] Bradycardia and other cardiac arrhythmias were seen during the late stages of toxicity secondary to the disruption of the sodium-potassium pump by TCAs.[11] Of the cases reported to the Animal Poison Control Center, death occurred in over 7% of the animals that displayed adverse signs.[11]

Similar signs were reported in a retrospective study of 22 dogs with serotonin toxicosis.[6] Trytophan can be found in an over-the-counter dietary supplement and is rapidly converted to serotonin after absorption from the GI tract. Clinical signs developed within 10 minutes to 4 hours after ingestion in 19 of the 21 dogs.[6] Again, neurologic and GI signs were most commonly seen. The neurologic signs consisted of mydriasis, transient blindness, depression, disorientation, hyperesthesia, hyperreflexia, tremors, ataxia, paresis, seizures, and coma.[6] The GI signs consisted of 385 vomiting, diarrhea, abdominal pain, ptyalism, flatulence, and bloat.[6] Seven dogs 386 developed hyperthermia (103.7° to 108° F rectally) and death occurred in three dogs.[6]

91.6 TOXICITY

SSRIs, TCA inhibitors, and MAOIs are absorbed rapidly from the GI tract following oral ingestion. TCAs have a narrow margin of safety with a therapeutic dosage generally falling in the range of 2 to 4 mg/kg and a toxic dose of 15 mg/kg.[11] MAOIs are also considered extremely toxic; however, the lethal dose in dogs and cats has yet to be published. In humans, an MAOI dose of only 2 mg/kg is considered extremely toxic.[1] On the other hand, SSRIs are considered relatively safe, with the minimum lethal dose reported to be greater than 100 mg/kg in dogs and 50 mg/kg in cats.[12] However, clinical signs consistent with serotonin syndrome were observed in dogs at doses ranging from 10 to 50 mg/kg.[13]

91.7 DIAGNOSIS AND TREATMENT

The diagnosis of serotonin syndrome is typically based on the history of ingestion of serotonergic drugs and compatible clinical signs. In an animal with no known history of ingestion, urine, blood, and gastric contents can be submitted to a toxicology laboratory for drug screening.

Any animal with a suspected overdose of serotonergic medication should undergo prompt decontamination (see Chapter 77, Approach to Poisoning and Drug Overdose). Emesis or gastric lavage should be performed in a clinically normal animal if treated within 15 minutes of ingestion. This should be followed by administration of activated charcoal to further minimize drug absorption. Repeated doses of activated charcoal every 6 hours are necessary with TCAs or other medications that undergo enterohepatic recirculation.[11] A cathartic, such as sorbitol, could be administered concurrently with the first dose of activated charcoal in animals. However, magnesium-containing cathartics should be avoided in animals that have ingested TCAs because of decreased GI motility, which may lead to toxic blood levels of magnesium.[11] Gastric lavage and administration of activated charcoal should not be performed in animals with clinical signs because of the risk of aspiration.

91.7.1 Box 91-1 Serotonergic Medications

91.7.1.1 Increase in Serotonin Production

L-Tryptophan

1–5-Hydroxytryptophan

91.7.1.2 Inhibition of Metabolism of Serotonin

MAO inhibitors: tranylcypromine

MAO-A inhibitors: moclobemide

MAO-B inhibitors: selegiline, clorgyline

91.7.1.3 Increased Serotonin Release

Amphetamines

MDMA (Ecstasy)

Cocaine

91.7.1.4 Serotonin Reuptake Inhibitors

SSRIs: fluoxetine, citalopram, paroxetine, sertraline, venlafaxine

Tramadol, fentanyl, pethidine, methadone, meperidine

Dextromethorphan

TCAs: amitriptyline, clomipramine, doxepin, imipramine

91.7.1.5 Stimulation of Serotonin Receptors

LSD

Lithium

Buspirone

Sumatriptan

LSD, Lysergic acid diethylamide; *MAO,* monoamine oxidase; *MDMA,* 3,4-methylenedioxymethamphetamine; *SSRIs,* selective serotonin reuptake inhibitors; *TCAs,* tricyclic antidepressants.

In animals with clinical signs of toxicosis, emergency treatment should be aimed at assessing airway patency, breathing, and circulatory and neurologic status (see Chapter 2, Patient Triage).[5] Life-threatening problems that can occur from serotonergic medication overdose include seizures, hyperthermia, and autonomic instability (tachycardia, bradycardia, hypertension, and hypotension). The intensity of therapy employed will depend on both the severity of ingestion and clinical signs. For example, in animals with mild neurologic and GI tract signs, supportive therapy should include intravenous fluids to correct and maintain hydration in addition to controlling GI tract signs. Diuresis will not enhance excretion, because these drugs are highly protein bound.

Animals with neurologic signs, such as agitation, tremors, and seizures, should be treated with intravenous diazepam (Valium) at 0.5 to 1 mg/kg as a bolus or 0.5 to 1 mg/kg/hr as a constant rate infusion (CRI).[14] If seizures cannot be controlled with diazepam, phenobarbital should be administered at 2 to 20 mg/kg IV[15] (see Chapter 186, Anticonvulsants). Hyperthermic animals should receive both active and passive cooling measures. Antipyretic agents are not indicated, because hyperthermia is a result of excessive muscular activity.[4] In severe refractory cases, neuromuscular paralysis could be induced followed by mechanical ventilation.[4,5]

Animals should be monitored closely for autonomic instability, including heart rate, with continuous electrocardiographic and blood pressure monitoring (either direct or indirect). Hypotension should be managed with direct-acting sympathomimetics (such as norepinephrine, phenylephrine, or epinephrine). Indirect agents, such as dopamine, need to be metabolized to epinephrine and norepinephrine.[4] In many overdoses, such as occurs with TCAs, catecholamine depletion occurs, rendering dopamine ineffective. On the other hand, tachycardia and hypertension may occur in MAOI overdose because of excessive concentrations of epinephrine and norepinephrine.[4] These animals should be treated with either a short-acting β-blocker such as esmolol (200 to 500 μg/kg IV followed by a CRI at 25 to 200 μg/kg/min) or nitroprusside (0.5 to 3 μg/kg/min) (see Chapter 178, Antihypertensives).[4,16,17]

Serotonin receptor antagonists, such as cyproheptadine and chlorpromazine, may have utility in the management of serotonin syndrome. Cyproheptadine, a nonspecific 5-$HT_{1A}$and 5-HT_2 receptor antagonist, has been shown to prevent the onset of clinical signs in animal models of serotonin syndrome.[18,19] However, evidence for its usefulness in human cases of serotonin syndrome is limited primarily to case reports, and its efficacy has not been fully established.[2,18] Cyproheptadine is available only in oral formulations and is well absorbed. It may be administered at dosages of 1.1 mg/kg in dogs or 2 to 4 mg PO in cats q4-6h.[6,20,21] When oral dosing is not possible or if there has been a recent administration of activated charcoal, cyproheptadine may be crushed and administered rectally.[19]

Chlorpromazine is also a 5-HT_2 receptor antagonist and may be considered as an antidote in animals with serotonergic medication overdose (0.5 mg/kg IV, IM, or SC q6h).[22] The main side effects of this medication are sedation and hypotension. Therefore close blood pressure monitoring is indicated both before and after administration. A study performed to evaluate the effects of serotonin receptor antagonists in a rat model of serotonin syndrome concluded that cyproheptadine (10 mg/kg) was more effective than chlorpromazine (20 to 40 mg/kg).[22] Nevertheless, both drugs prevented death at the higher dosages.[23] Other serotonin receptor antagonists investigated in animal models include ritanserin, pipamperone, risperidone, and ketanserin.[23,24]

91.8 PROGNOSIS

The prognosis for animals with serotonin syndrome is variable depending on the quantity ingested, clinical signs, treatment, and concurrent administration of other highly protein-bound medications.[16] Animals with minimal signs generally have a good prognosis, but in animals with severe neurologic signs, hyperthermia, and GI signs, the prognosis should be considered guarded.

91.9 SUGGESTED FURTHER READING*

J Brent: Monoamine oxidase inhibitors and the serotonin syndrome. In LM Haddad, MW Shannon, JF Winchester (Eds.): *Clinical treatment of poisoning and drug overdose*. 1998, Saunders, Philadelphia, *A good overview of MAOIs and serotonin syndrome*.

LR Johnson: Tricyclic antidepressant toxicosis. *Vet Clin North Am Small Anim Pract*. **20**, 1990, 393, *A review of TCAs and a case series of TCA overdose in animals reported to the animal poison control center*.

TA Wismer: Antidepressant drug overdose in dogs. *Vet Med*. **95**, 2000, 520, *A review of antidepressant medications, clinical signs, and current recommendations for treatment of overdoses with TCAs, MAOIs, and SSRIs in dogs*.

* See the CD-ROM for a complete list of references

92 Chapter 92 Anticholinesterase Intoxication

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92.1 KEY POINTS

- Organophosphate and carbamate insecticides are in common industrial and household use.
- Acute toxicity is due to inhibition of acetylcholinesterase at cholinergic synapses throughout the body.
- Supportive care is extremely important for recovery.
- The cornerstone of antidotal therapy for acute toxicity is atropine.
- Intermediate syndrome is a manifestation of acute organophosphate toxicity in which proximal limb, neck, and respiratory muscle weakness predominates.
- Organophosphate-induced delayed neuropathy occurs 1 to 4 weeks after a single organophosphate exposure or after long-term, low-dose organophosphate exposure in which pelvic limb weakness predominates. 388
- With appropriate management, prognosis is fair to good in all syndromes.

92.2 INTRODUCTION

Organophosphate and carbamate compounds are used commonly as industrial and household insecticides, and are also used in some deworming products and medications. Intoxication with these compounds is common in veterinary patients. As pesticides, they are widely available in powder, granular, or aerosol forms. Exposure may occur by ingestion, inhalation, or dermal contact. The lethal doses (LD_{50}) vary widely by compound.

92.3 MECHANISM OF ACTION

Organophosphate and carbamate compounds inhibit the enzyme acetylcholinesterase (AchE) at the synaptic cleft; organophosphates bind AchE much more strongly than do carbamates. AchE is responsible for hydrolysis of acetylcholine (Ach) in cholinergic synapses of the autonomic nervous system, neuromuscular junction, and central nervous system (CNS). When an organophosphate or a carbamate inhibits AchE, excessive Ach accumulates in the synapse, leading to overstimulation of the postsynaptic neuron or muscle. This overstimulation is the cause of the classic symptoms of acute organophosphate or carbamate toxicity, listed in the next section. Within 12 to 24 hours of exposure, organophosphate compounds (but not carbamates) can become permanently bound to AchE, a process called *aging*. Organophosphates have been associated with two other distinct syndromes, intermediate syndrome and organophosphate-induced delayed neuropathy. Exactly how neuropathy. Exactly how the organophosphate toxin contributes to the development of these two syndromes is unclear, but it does not appear to be directly related to AchE inhibition.

92.4 ACUTE ORGANOPHOSPHATE AND CARBAMATE TOXICITY

Acute organophosphate or carbamate toxicity generally occurs within 0.5 to 6 hours after ingestion or inhalation of a product; dermal absorption time can vary, but clinical signs may be present within a few hours.

92.4.1 Clinical Signs

Classic clinical signs of acute toxicity are broken down into three basic categories:

1. Muscarinic signs: Diarrhea, urination, miosis, bronchospasm, emesis, lacrimation, and salivation (DUMBELS[1]). Bronchospasm and bronchorrhea (excessive bronchial secretions) can lead to severe dyspnea and hypoxemia. Bradycardia is common.
2. Nicotinic signs: Muscle tremors, twitching, and eventually weakness to paralysis occur.
3. CNS signs: Seizures, convulsions, and obtundation to coma occur.

Not all signs are present in all patients. Patients may be tachycardic if Ach effects at sympathetic ganglia predominate. Ventricular arrhythmia was associated with organophosphate toxicity in one cat.[2]

92.4.2 Diagnosis

A diagnosis of acute organophosphate or carbamate intoxication is made using patient history, clinical signs, and toxicologic data. Known or suspected organophosphate or carbamate exposure by ingestion, topical application, or inhalation should raise the clinician's index of suspicion. A test dose of atropine can help distinguish muscarinic signs due to acute organophosphate or carbamate toxicity from similar signs caused by other diseases. The patient with anticholinesterase toxicity should not respond to a single test dose of atropine (0.02 mg/kg IV); if muscarinic signs resolve with this dose, the diagnosis is not likely to be organophosphate or carbamate toxicity.[3,4]

Clinicopathologic data are nonspecific, but azotemia, hematuria, leukocytosis, elevated creatinine kinase levels, hypokalemia, and hyperglycemia are common.[5] Toxicologic evaluation may be performed on blood, gastric contents, urine, or source material to determine the involved toxin. Also, whole blood should be submitted to determine blood cholinesterase levels. Contact a veterinary toxicology laboratory to confirm ideal sample handling procedures. Blood likely needs to be heparinized and transported on ice. Normal blood cholinesterase levels vary significantly by species, so samples should be sent to a laboratory familiar with various reference ranges. Cholinesterase activity less than 50% of normal is suspicious for intoxication, and activity less than 25% of normal is confirmatory.[3,6,7]

92.4.3 Treatment

92.4.3.1 Decontamination

Decontamination strategies should be employed in patients with acute organophosphate or carbamate intoxication, and in patients known to have ingested a toxin even if they are not yet showing signs. Emesis should never be induced in patients with an altered state of consciousness, or in those for whom aspiration is a significant risk. Activated charcoal is useful for organophosphates and carbamates. All patients with the potential for topical exposure should be bathed with soap and water as soon as possible, and dried completely to prevent hypothermia (see Chapter 77, Approach to Poisoning and Drug Overdose).

92.4.3.2 Supportive Care

Supportive treatment of the intoxicated patient is imperative. Patients with organophosphate or carbamate toxicity can be dehydrated or hypovolemic from diarrhea, excessive salivation, and sustained muscle activity. Intravenous fluid support should be provided as patient perfusion and hydration parameters dictate. Electrolyte concentrations and acid-base status should be evaluated and corrected as needed. Seizures should be treated with diazepam (0.5 to 1 mg/kg IV to effect) or barbiturates. Excessive bronchial secretions and aspiration of saliva can lead to severe lower airway obstruction and subsequent hypoxemia. Hypoxemic patients should be treated with supplemental oxygen; tracheal intubation and positive-pressure ventilation may be required if oxygen supplementation alone is inadequate. Weakness can be so severe as to cause compromised respiratory muscle function, and patients with severe hypoventilation or apnea require tracheal intubation and positive-pressure ventilation.

92.4.3.3 Traditional Antidotes

Atropine is the mainstay of antidotal treatment for organophosphate or carbamate toxicity. Treat muscarinic signs such as bradycardia or excessive bronchial secretions with an initial dose of atropine at 0.1 to 2 mg/kg (¼ IV, remainder SC).[3, 8-10] Repeat 0.1 to 0.25 mg/kg IV q20-30min until clinical signs of atropinization occur: mydriasis, flushed skin, dry mouth, and mild sinus tachycardia (if the patient already is tachycardic, it cannot be used as an end point of atropinization). The total atropine dosage required to achieve these goals varies by the severity of intoxication. In humans, atropinization is maintained either with repeated administration as above, or with a constant rate infusion (CRI) at 0.02 to 0.08 mg/kg/hr.[4] Patients should be monitored closely with continuous electrocardiograms and frequent blood pressure measurements, and atropine should be used cautiously in patients with ventricular arrhythmias because of the potential for ventricular fibrillation.

Pralidoxime (2-pyridine aldoxime methiodide [2-PAM]) is an antidote for the nicotinic signs of acute, moderate to severe anticholinesterase toxicity. It has little effect on muscarinic or CNS signs. Therefore atropine must be used to treat muscarinic signs, and diazepam is indicated for seizures (see Supportive Care in previous section). The efficacy of 2-PAM is debated in human clinical literature, and the drug may be less effective without concurrent atropinization. 2-PAM reactivates AchE by binding AchE and inducing a shape change, thereby dislodging the toxin so that it may be hydrolyzed and excreted more rapidly. It may also bind free organophosphate toxin and exert some anticholinergic effects.[4] Because 2-PAM has some anticholinesterase activity, it can worsen signs in less severely intoxicated animals, and its use in mildly affected patients is not recommended. The dose is 10 to 20 mg/kg SC or IV as a slow infusion q12h.[9,10] Refer to the package insert for other information.

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2-PAM use in carbamate toxicity is controversial, because carbamates bind less avidly to AchE than do organophosphates, and are therefore more likely to be hydrolyzed and excreted without the aid of an antidote. Because pralidoxime has some anticholinesterase activity, it could theoretically antagonize AchE more severely than the carbamate itself. Experimentally, 2-PAM has been beneficial in severe, acute carbamate toxicity.[11] The important exception is intoxication with the carbamate carbaryl, in which case 2-PAM consistently worsens subjects' signs and is therefore contraindicated.[1,11,12]

2-PAM can be detrimental in cases of subacute to chronic organophosphate toxicity, because organophosphate molecules become permanently bound to AchE as they age. Once the toxin-AchE complex has aged, 2-PAM cannot dislodge the toxin; 2-PAM's anticholinesterase properties may then predominate, exacerbating signs of toxicity. Aging occurs at different rates for different organophosphate molecules; in general, aging occurs more rapidly in O-O-dimethyl organophosphates (significant aging within 12 hours) than it does in O-O-diethyl organophosphates (may be partially reversible with 2-PAM for up to 24 to 48 hours).[13]

Moreover, the clinician must take all factors into consideration when deciding whether to treat a patient with 2-PAM. Factors to consider include severity of clinical signs, known or suspected identity of the toxin, and time elapsed since exposure. Most importantly, all patients receiving 2-PAM should be monitored closely during administration for exacerbation of clinical signs; if signs worsen, therapy should be discontinued.

92.4.3.4

Experimental Therapies

Diphenhydramine has antinicotinic effects. One experimental study in rats showed significant improvement in survival with high doses of diphenhydramine administered concurrently with the organophosphate.[14] Diphenhydramine is not considered a standard therapy in organophosphate toxicity in human medicine, and its efficacy as an antidote has not been clinically proven. Its routine use cannot therefore be recommended, although refractory or very severe cases may benefit. Additionally, it may be used in place of 2-PAM if this proven antidote is unavailable. The dosage used in an experimental canine study of chronic organophosphate exposure was 4 mg/kg PO q8h.[15]

Some small clinical studies in humans suggest that serum alkalinization to a pH of 7.50 may improve survival in patients suffering from acute organophosphate toxicity.[16] No large clinical studies have been performed in humans, and no information regarding alkalinization is available for veterinary patients. Cautious alkalinization with sodium bicarbonate may be considered for severely affected patients but cannot be recommended as a standard therapy. Alkalinization should not be performed in clinics without the ability to measure pH, bicarbonate concentration, and partial pressure of carbon dioxide, and should be performed with extreme caution in patients with existing respiratory acidosis.

Magnesium sulfate has been shown to improve survival and decrease length of hospital stay in one small, single-blinded, controlled clinical study of acute organophosphate toxicity in humans.[17] Magnesium sulfate was administered as a CRI for the first 24 hours of hospitalization and did not decrease requirements for atropine or pralidoxime, nor did it increase measured cholinesterase activity. This treatment improved survival even though patients' serum magnesium levels were normal before therapy. The mechanism of benefit is not known. No clinical information is available about treatment of veterinary patients with magnesium sulfate for organophosphate toxicity, and magnesium sulfate therapy carries significant risks; therefore it should be used with extreme caution for this indication. Any patient receiving magnesium sulfate must be monitored with continuous electrocardiograms and frequent blood pressure measurements; serum magnesium levels (total and ionized) should be performed frequently to prevent hypermagnesemia.

There is experimental evidence that very high-dose ranitidine may be useful as an antidote to anticholinesterase toxins.[18] Ranitidine has weak anticholinesterase effects and competes with the toxin for AchE in a manner similar to that of pralidoxime. However, clinical studies have not been done to confirm ranitidine's clinical efficacy and safety at the necessary dosage; therefore its use as an antidote is inappropriate until further information is available.

92.4.4 Prognosis

If the patient survives the acute phase of toxicity, the prognosis is good as long as toxin sources are removed from the environment. Patients can progress to intermediate syndrome after resolution of acute signs, but this clinical course is rare in veterinary medicine.

92.5 INTERMEDIATE SYNDROME

Intermediate syndrome is a form of organophosphate toxicity in which signs of neuromuscular weakness predominate. It generally occurs 8 hours to 4 days after organophosphate exposure, either in patients that have not manifested classic signs of acute toxicity or after those signs have resolved. It is hypothesized that the weakness is due to neuromuscular junctionopathy secondary to prolonged AchE inhibition. Many organophosphate toxins have been associated with the syndrome in humans. Although intermediate syndrome has been reported in up to 22% of people with acute organophosphate toxicity,[19-22] it has been reported only once in a small animal patient.[23]

92.5.1 Clinical Signs

Intermediate syndrome is characterized by neuromuscular weakness, particularly of the proximal limbs, neck, and muscles of respiration. Cranial nerve and deep tendon reflexes may be decreased. Gag reflex may be poor to absent if cranial nerves are involved. Significant respiratory depression is common, and mechanical ventilation often is required for severe hypoventilation.[19-26] The weakness resolves spontaneously over the course of weeks in patients that survive the initial crisis.

92.5.2 Diagnosis

The diagnosis of intermediate syndrome is made using patient history of known or possible organophosphate exposure, signs of muscular weakness most profound in the neck and proximal limbs, and toxicologic testing. Blood cholinesterase activity evaluation will distinguish this syndrome from myasthenia gravis and other neuromuscular diseases. See the discussion of diagnosis in the acute toxicity section for more information about toxicologic testing.

92.5.3 Treatment

92.5.3.1 Decontamination

Because of the delayed onset of intermediate syndrome, induction of emesis and administration of activated charcoal may or may not be beneficial. If the patient has a decreased gag reflex or is obtunded, induction of emesis or oral administration of activated charcoal are contraindicated regardless of time elapsed since ingestion. Any patient with topical exposure should be bathed with soap and water as soon as possible, and dried completely to prevent hypothermia (see Chapter 77, Approach to Poisoning and Drug Overdose).

92.5.3.2 Supportive Care

Supportive care is of utmost importance in intermediate syndrome. Intravenous fluid therapy should be provided as needed to treat hypovolemia or dehydration, and maintenance fluid therapy provided to patients unable to eat and drink. Anorectic patients will require nutritional support by enteral or parenteral feeding (see Chapters 13 and 14, Enteral Nutrition and Parenteral Nutrition, respectively). Recumbent patients will require intensive nursing care with well-padded bedding and frequent repositioning to prevent decubitus ulcers and urine scald. Patients with significant respiratory depression require tracheal intubation and mechanical ventilation for survival.

92.5.3.3 Antidotal Therapy

Atropine is not indicated for intermediate syndrome, because muscarinic signs generally are not present. 2-PAM is used in people with intermediate syndrome,[22] because some AchE inhibition may still be present.[13] Please refer to the treatment section for acute organophosphate toxicity for information regarding pralidoxime.

92.5.3.4 Experimental Therapy

Diphenhydramine has antinicotinic effects. One experimental study in dogs with long-term exposure to the organophosphate fenthion found that diphenhydramine reversed the electromyographic changes seen in the toxicity, suggesting it may be useful in patients with intermediate syndrome.[15] Diphenhydramine is not considered a standard therapy in organophosphate toxicity in humans, and its efficacy for this indication has not been clinically proven. Its routine use cannot therefore be recommended, although refractory or very severe cases may benefit. The dosage used in this canine study was 4 mg/kg PO q8h.

92.5.4 Prognosis

The prognosis for recovery from intermediate syndrome is good if the patient is supported appropriately through the initial neuromuscular crisis. However, because the syndrome can induce severe hypoventilation and may predispose to aspiration pneumonia due to decreased gag reflex and recumbency, overall prognosis for severely affected patients is guarded until ventilation is adequate, a gag reflex is present, and the patient can support itself sternally. In the single report of intermediate syndrome in the veterinary literature, the affected dog fulfilled all three of these criteria by day 7 of hospitalization and made a complete recovery.[23] Clinical signs generally resolve completely over the course of weeks.

92.6 ORGANOPHOSPHATE-INDUCED DELAYED NEUROPATHY

Organophosphate-induced delayed neuropathy (OPIDN; also called *organophosphate-induced delayed polyneuropathy,* or*OPIDP*) is a toxic syndrome characterized by pelvic limb weakness, ataxia, and dull mentation. It is associated most commonly with long-term organophosphate exposure, but can be seen after a single toxic exposure to certain organophosphates; the syndrome usually manifests 1 to 4 weeks after introduction of the toxin. Often, long-term exposures that cause OPIDN are of inadequate dosage to cause classic acute signs of organophosphate toxicity. Clinical signs of OPIDN are caused by damage to or inadequate maintenance of axons. Axonal degeneration is associated with organophosphate binding to an enzyme called *neuropathy target esterase,* although the exact mechanism of axonal injury is unclear. Muscles innervated by the longest axons (those of the pelvic limbs) are affected most severely.[4,22,27] OPIDN is seen most commonly in humans with long-term occupational exposure, and has been documented in cats both in the experimental[28] and clinical settings.[29,30] The veterinary literature contains no clinical reports of OPIDN in dogs.

Note that OPIDN is a different toxic entity than intermediate syndrome. Although intermediate syndrome is a manifestation of acute toxicity seen within 7 to 96 hours of organophosphate exposure, OPIDN occurs 1 to 4 weeks after an exposure that is often long term. In addition, although intermediate syndrome manifests as weakness in primarily the cervical, thoracic limb, and respiratory muscles, OPIDN most profoundly affects the pelvic limbs.

92.6.1 Clinical Signs

The patient may or may not have exhibited signs of a classic, acute organophosphate toxicity 1 to 4 weeks before the onset of OPIDN. Patients with OPIDN initially exhibit weakness of distal musculature, particularly in the pelvic limbs. Weakness most profound in the pelvic limbs, generalized weakness, decreased spinal reflexes, decreased conscious proprioception, hyperesthesia, muscle wasting, mydriasis, anorexia, and dull mentation were noted in the clinical feline reports, although none of the three cats manifested every clinical sign.[29,30] Muscarinic signs are not present in this syndrome.

92.6.2 Diagnosis

A diagnosis of OPIDN is made using patient history of known or possible organophosphate exposure, signs of muscular weakness most profound in the pelvic limbs, and toxicologic testing. History may include periodic home or garden insecticide spraying, topical insecticide application, or other long-term exposures less obvious than a single ingestion. Blood cholinesterase activity evaluation will distinguish this syndrome from myasthenia gravis and other neuromuscular diseases. See the discussion of diagnosis in the acute toxicity section for more information about toxicologic testing.

92.6.3 Treatment

92.6.3.1 Decontamination

GI decontamination is beneficial only when exposure is ongoing. Animals with ongoing topical exposure may 390
benefit from GI decontamination in the event that they have ingested some toxin through grooming behavior. 391
If the patient is obtunded, induction of emesis and oral administration of activated charcoal are contraindicated. All patients with topical exposure should be bathed with soap and water as soon as possible, and dried completely to prevent hypothermia (see Chapter 77, Approach to Poisoning and Drug Overdose).

92.6.3.2 Supportive Care

Supportive care is the only effective therapy for OPIDN, because there is no known effective antidote. Intravenous fluid therapy should be provided as needed to treat hypovolemia or dehydration and maintenance fluid therapy provided to patients unable to eat and drink. Anorectic patients will require nutritional support by enteral or parenteral feeding (see Chapters 13 and 14, Enteral Nutrition and Parenteral Nutrition, respectively). Diazepam used for appetite stimulation in cats with OPIDN has been associated with worsening of clinical signs[29] and is therefore not recommended. Recumbent patients will require intensive nursing care with well-padded bedding and frequent repositioning to prevent decubitus ulcers and urine scald. Removal of toxin from the patient's environment is the most important therapy for animals with OPIDN.

92.6.4 Prognosis

In the three cats reported in the clinical veterinary literature, all recovered completely over the course of weeks and were clinically normal at reexamination months later.[29,30] However, the prognosis in humans with OPIDN is guarded. Although some people recover completely over the course of months to years, many develop hypertonic paralysis of the pelvic limbs that never completely recedes.

92.7 OTHER SYNDROMES ASSOCIATED WITH ORGANOPHOSPHATE TOXICITY

92.7.1 Acute Pancreatitis

Organophosphates can cause acute pancreatitis in the dog. Canine pancreas contains the enzyme butyrylcholinesterase, which can be inhibited by anticholinesterase agents, leading to acinar cell overstimulation and acute pancreatitis.[31] Feline pancreas does not contain butyrylcholinesterase, and experimental administration of an organophosphate did not lead to pancreatitis in this species.[31] Acute pancreatitis is seen occasionally in humans with clinical anticholinesterase intoxication[1,32] and should be considered a risk in dogs with organophosphate toxicity.

92.7.2 Behavioral Changes

There is a single case report of a cat with significant behavioral abnormalities that concurrently had the organophosphate diazinon in its serum.[33] The cat exhibited disorientation, vocalization, and acute, violent aggression. The cat's behavior returned to normal after removal of the organophosphate source.

92.8 SUGGESTED FURTHER READING*

DJ Blodgett: Organophosphate and carbamate insecticides. In ME Peterson, PA Talcott (Eds.): *Small animal toxicology*. ed 2, 2006, Saunders, St Louis, *A fantastic small animal–specific toxicology book, well laid out and easy to read, with good depth in physiology. The perfect single toxicology reference for the small animal veterinarian.*

SR Hansen: Management of organophosphate and carbamate insecticide toxicoses. In JD Bonagura (Ed.): *Kirk's current veterinary therapy XIII: Small animal practice*. ed 13, 2000, Saunders, Philadelphia, *concise review of the management of these toxicities*.

K Hopper, J Aldrich, SC Haskins: The recognition and treatment of the intermediate syndrome of organophosphate poisoning in a dog. *J Vet Emerg Crit Care*. **12**, 2002, 99, *Details of the only clinical case of intermediate syndrome in the veterinary literature with a discussion that includes a good review of mechanical ventilation of the hypoventilating patient.*

GL Meerdink: Anticholinesterase insecticides. In KH Plumlee (Ed.): *Clinical veterinary toxicology*. 2004, Mosby, St Louis, *A chapter that provides information on organophosphate and carbamate toxicity in small and large animal veterinary patients. Comprehensive and a good review.*

DE Rusyniak, KA Nanagas: Organophosphate poisoning. *Semin Neurol*. **24**, 2004, 197, *A review article that provides a concise overview of the pathophysiology and clinical signs of all three manifestations of organophosphate toxicity, and discusses treatment of classic, acute toxicity*.

* See the CD-ROM for a complete list of references.

93 Chapter 93 Ivermectin Toxicity

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93.1 KEY POINTS

- Ivermectin doses as low as 90 to 100 mg/kg have resulted in clinical signs in sensitive dogs; however, the licensed dosage for heartworm prevention is substantially lower.
- Common clinical signs of toxicity include ataxia, vocalization, disorientation, hyperesthesia, blindness, weakness, mydriasis, and bradycardia.
- There is no antidote, so management is primarily supportive care.
- Prognosis for eventual recovery is good. However, severely affected patients may require prolonged medical and nursing care, and the clinical course may be confounded by complications.

93.2 IVERMECTIN: THE DRUG

93.2.1 Description

Ivermectin is a broad-spectrum antiparasitic drug that is used commonly in veterinary medicine and generally has a wide margin of safety. It is a fermentation by-product of *Streptomyces avermitilis* bacteria, and the compound is comprised of 80% or more avermectin B_{1a} and 20% or less of avermectin B_{1b}. Although it bears structural homology to the macrocyclic lactone class of antibiotics, ivermectin has no antibacterial or antifungal activity. Ivermectin is used most commonly as an antiparasitic agent against nematode infestations and external arthropod parasites (e.g., mites).[1] It is licensed for use in dogs and cats as a heartworm preventive, prescribed at 6 and 24 μg/kg PO, respectively, to be administered once per month. It is also used in dogs, off-label, to manage ectoparasites and endoparasites at a dosage of 50 to 300 μg/kg PO or SC.[2] Other forms of avermectin that have similar mechanisms of action and toxicity and might result in similar clinical signs include moxidectin, eprinomectin, selamectin, milbemycin, and doramectin.

93.2.2 Mechanism of Action

Ivermectin is an agonist of invertebrate-specific, glutamate-activated, inhibitory chloride channels; it causes flaccid paralysis and subsequent death in nematodes and mites. Ivermectin's toxic effect in mammals is due to the similarity of these invertebrate-specific channels to vertebrate γ-aminobutyric acid ($GABA_A$)-gated chloride channels that inhibit interneurons in the central nervous system (CNS). At higher concentrations, ivermectin potentiates these vertebrate $GABA_A$-gated chloride channels. This can have a toxic effect as CNS concentrations of ivermectin increase and cause hyperpolarization of cell membranes, preventing neuronal depolarization.[1,3]

93.2.3 Ivermectin Sensitivity

The multidrug-resistance *(mdr1)* gene codes for a large transmembrane protein called P-glycoprotein (P-gp), which is an integral part of the blood-brain barrier. P-gp is an efflux drug-transport pump that moves a variety of drugs, including ivermectin, from the brain back into the blood. A 4-base pair deletion mutation of the *mdr1* gene that encodes P-gp has been found in some ivermectin-sensitive animals, including Collies and other herding dogs. P-gp prevents high levels of ivermectin, and other lipophilic compounds, from accumulating in the CNS by actively pumping the drug out of the cells and back into the blood.[4] Forty-eight percent of 25 Collie dogs tested in France were homozygous for the mutant allele that confers ivermectin sensitivity,[5] and it has been estimated that as many as 30% to 40% of Collie dogs in the United States are sensitive; this relatively high prevalence should be considered when treating Collie dogs with avermectins.

93.2.4 Pharmacokinetics

Ivermectin is absorbed rapidly when administered either subcutaneously or orally.[2] Gastrointestinal (GI) absorption is the more rapid, about 95% is absorbed, and peak plasma concentrations are achieved within 2 to 4 hours after oral administration. Ivermectin is metabolized via oxidation in the liver and excreted in the bile to the feces; less than 5% is excreted in the urine. Its half-life in dogs is approximately 2 days.[1]

93.2.5 Toxicity

Most dogs tolerate ivermectin dosages up to 2.5 mg/kg PO before they exhibit clinical signs of toxicity.[3] No adverse effects were detected in Beagle dogs when administered up to 2 mg/kg PO as a single dose; the lethal dose (LD_{50}) in Beagle dogs has been reported as 80 mg/kg.[2,6] However, in dogs that are sensitive to ivermectin, doses as low as 90 to 100 μg/kg have resulted in signs including ataxia and depression. Toxicity has been documented repeatedly in Collie dogs at doses of 100 to 500 μg/kg; ivermectin sensitivity has also been reported in two Australian Shepherds and suspected in an Old English Sheepdog cross.[1,6]

Published ivermectin tolerances for cats are varied, ranging from 0.2 to 1.3 mg/kg PO or SC,[1] to a narrower oral dosage range of 0.5 to 0.75 mg/kg. However, toxicosis has been reported in kittens exposed to as little as 300 to 400 μg/kg SC.[3] Younger animals do not have a fully developed blood-brain barrier and as a result may be more susceptible to ivermectin toxicity.

93.2.5.1 Box 93-1 Clinical Signs Associated With Ivermectin Toxicity

93.2.5.1.1 Common Clinical Signs in Dogs[3,6]

- Ataxia
- Weakness
- Vocalization
- Hyperesthesia
- Hyperactivity

Paddling

Hyperthermia

Hypothermia

Disorientation

Obtundation

Apparent blindness

Mydriasis

Vomiting

Ptyalism

Bradycardia

93.2.5.1.2 Common Clinical Signs in Cats[3]

Ataxia

Vocalization

Hypothermia

Disorientation

Dementia

Blindness

Mydriasis

Head pressing

- Body tremors
- Bradycardia

93.2.5.1.3 Severe Intoxication in Dogs and Cats

- Seizures
- Hypoventilation
- Cyanosis
- Coma
- Death

93.3 CLINICAL SIGNS

Commonly reported signs of ivermectin toxicity include ataxia, vocalization, disorientation, hyperesthesia, blindness, weakness, mydriasis, and bradycardia (Box 93-1). The severely affected animal is typified by early signs of agitation, disorientation, and even seizures, followed by generalized weakness, which is usually accompanied by stupor or coma. Complications such as hypoventilation secondary to respiratory muscle weakness and aspiration pneumonia are of concern, because they require a higher level of medical care and greater financial commitment from the owner. Signs may manifest as early as 2 to 4 hours after exposure, or may be delayed in onset by up to 24 hours; they may progress in severity for several days to a week following intoxication. This necessitates close observation of the intoxicated patient for the 5 to 7 days after exposure. Significant ivermectin toxicity is associated with a protracted clinical course; there are reports of dogs requiring medical care for 3 to 5 weeks.[6,7]

Therapeutic or toxic doses of ivermectin cause death of microfilaria. In situations of a large microfilarial burden, this can lead to hypotension from maldistributive or anaphylactic shock.

93.4 DIAGNOSIS

Diagnosis of ivermectin toxicity depends primarily on a history of recent exposure and the presence of clinical signs. There are no gross pathologic lesions associated with intoxication. If a definitive diagnosis is required, samples of liver, adipose, or serum can be submitted for ivermectin detection. However, there is little correlation between serum concentration and severity of clinical signs, which are more likely reflective of the patient's CNS concentration than the systemic concentration of the drug.

If a patient's exposure history is not known, other intoxicants that should be considered include organophosphate and carbamate insecticides, sedative drugs such as barbiturates and opiates, centrally acting muscle relaxants, and tremorogenic mycotoxins.[3]

93.5 TREATMENT

If oral exposure has occurred within 2 to 3 hours of presentation and the patient is neurologically normal, emesis can be induced (see Chapter 77, Approach to Poisoning and Drug Overdose). The drug undergoes enterohepatic circulation, so repeated doses of activated charcoal may be effective for decreasing serum levels of the drug.

There is no antidote, so supportive care and symptomatic treatment are the most important components when treating ivermectin toxicosis. Severely affected patients may require recumbent-patient nursing care, intravenous (IV) fluid therapy, IV nutritional support, and mechanical ventilation. Stuporous or comatose animals should be evaluated frequently for an adequate gag reflex. If the gag reflex is diminished or absent, endotracheal intubation is indicated to protect the airway. The principles of ventilator patient care as outlined in Chapter 216, Care of the Ventilator Patient, should be applied to management of the recumbent intubated patient. It is important to monitor blood gases or capnography to assess ventilation. Hypercapnia of 60 mm Hg or higher is generally considered an indication for mechanical ventilation. Patients should be monitored closely for the first week after intoxication, because progression of clinical signs can be slow.

Anticonvulsant therapy for seizure control should include phenobarbital, with the addition of pentobarbital if convulsions or tremors are persistent. Historically, it has been recommended that diazepam, and other benzodiazepines, be avoided in patients with ivermectin toxicosis, because ivermectin is a $GABA_A$ agonist and it was believed to bind very near the benzodiazepine receptor. As such, diazepam might potentiate the effects of ivermectin and prolong recovery.[3,6] Although not proven, it has been suggested that ivermectin and benzodiazepines may act on different $GABA_A$ receptor subtypes, which would nullify this argument for avoiding the use of diazepam for sedation or seizure control. Alternative drugs that have been proposed for sedating ivermectin-intoxicated patients include phenobarbital, pentobarbital, propofol, and etomidate. The barbiturates act on the $GABA_A$ receptor at a more distant binding site from that of ivermectin. The effects of propofol and etomidate on the GABA receptor have not been fully elucidated, but these drugs may be safer alternatives.[6]

Physostigmine, a reversible cholinesterase inhibitor, was used in ivermectin-sensitive Collies at 1 mg IV administered slowly and was reported to counteract the effects of ivermectin for 30 to 90 minutes.[1] An alternative dosage proposed is 0.06 mg/kg IV, administered very slowly. However, physostigmine should be used with caution because of its potential for toxicity, and it can worsen clinical signs in mildly affected dogs.[3] There is a single reported use of neostigmine in the treatment of a massive overdose of ivermectin in two kittens and an adult cat; although the adult cat did survive, there is insufficient data to support its use.[8]

Picrotoxin is a GABA antagonist that may cause seizures when given intravenously. It is an experimental drug and is not recommended for use in the treatment of ivermectin toxicosis.

93.6 PROGNOSIS

It may require days to weeks of intensive supportive care for affected patients to recover, and severely affected patients may require mechanical ventilation for hypoventilation or aspiration pneumonia. Prognosis for eventual recovery is good, even in cases of severe intoxication; however, the clinical course can take several weeks and may be confounded by complications. Unfortunately, long-term hospitalization and high costs may influence owner decisions.

93.7

Suggested Further Reading[*]

K Hopper, J Aldrich, SC Haskins: Ivermectin toxicity in 17 Collies. *J Vet Intern Med*. **16**, 2002, 89, *A retrospective case series that provides a concise overview of ivermectin toxicity in Collies; risks and benefits of various treatment strategies discussed clearly*.

R Lovell: Ivermectin and piperazine toxicosis in dogs and cats. *Vet Clin North Am Small Anim Pract*. **20**, 1990, 453, *An overview of ivermectin intoxication; provides a comprehensive list of landmark references on this topic*.

KH Plumlee: Antiparasitic agents. In ME Peterson, PA Talcott (Eds.): *Small animal toxicology*. ed 2, 2006, Saunders, St Louis, *A concise chapter that addresses the clinical signs and recommended treatments for the most common antiparasitic agents used in small companion animal medicine*.

[*] See the CD-ROM for a complete list of references

94 Chapter 94 Pyrethrins

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94.1 KEY POINTS

- Pyrethrins and their derivatives, pyrethroids, are insecticides frequently used in flea and tick control products for dogs and cats.
- Cats are more susceptible to pyrethrin and pyrethroid intoxication than dogs, in part because of inefficiency of the feline liver for glucuronide conjugation.
- Most severe toxicity cases in cats result from application of highly concentrated pyrethroid spot-on flea control products labeled for use in dogs only.
- The toxic effect predominantly results from the interaction of pyrethrins and pyrethroids with voltage-sensitive sodium channels (VSSCs) in the central and peripheral nervous systems.
- Prominent clinical signs include mydriasis, hypersalivation, twitching, tremors, and seizures.
- History of exposure to the toxin is of great importance when making a diagnosis, although determination of pyrethrin and pyrethroid levels on blood or tissue samples is possible.
- No antidote is available and treatment consists of decontamination, pharmacologic control of tremors or seizures, and supportive measures according to clinical abnormalities.
- Dogs and cats generally have a good prognosis after exposure to pyrethrins and pyrethroids as long as appropriate medical attention is provided.

94.2 INTRODUCTION

Pyrethrins and their derivatives, pyrethroids, are insecticides frequently used in flea control products for dogs and cats. Pyrethrins, six distinct insecticidal constituents contained in the extract of the chrysanthemum flower, were structurally modified to increase their environmental stability.[1] The resultant derivatives, termed *pyrethroids,* have been used extensively in agricultural, house, and garden formulations over the last 3 decades and make up around one fourth of the world insecticide market.[1] The pyrethrins and pyrethroids have lower environmental contamination and vertebrate toxicity than other insecticides such as organophosphates and carbamates. The usefulness of an insecticide that is used clinically (i.e., topical flea products used in companion animals) is based on its differential toxic effect on the target versus the host organism: high potency against insects versus low toxicity for mammals. Selectivity ratios (mammalian oral lethal dose [LD_{50}]-to-insect topical LD_{50}) for pyrethroids are typically greater than 1000, but are less than 100 for other insecticides.[2] Flea products, particularly spot-ons containing high concentrations of pyrethroids, are the main source of toxicosis in small animals, especially in cats. Other formulations such as sprays, dips, powders, shampoos, gels, collars, pour-ons, and aerosol bombs are additional sources of toxicity. Substances contained in these products are pyrethrin I, allethrin, fenvalerate, resmethrin, sumethrin, and permethrin.

94.3 STRUCTURES OF PYRETHRINS AND PYRETHROIDS

The insecticide pyrethrum is a crude extract from chrysanthemum flowers (*Chrysanthemum cinerariifolium* and *C. cineum*). It exerts its insecticidal activity as a result of six distinct substances contained within: pyrethrin I and II, cinerin I and II, and jasmolin I and II. They are collectively termed *pyrethrins,* the most potent being pyrethrin I. Structurally they are very similar esters of a cyclopropane carboxylic acid (acid moiety) and a cyclopentenolone alcohol (alcohol moiety). Pyrethroids are synthetic derivatives of the natural pyrethrins and were generated primarily to achieve more photostability while retaining the desired insecticidal and toxicologic properties. The most important compounds are listed in Box 94-1.

Because pyrethroids contain two to three chiral carbons, four to eight stereoisomeric compounds exist for each substance. Not all stereoisomers of a given compound have insecticidal activity or cause mammalian neurotoxicity. The 1R,*cis* configuration of permethrin, for example, is toxic to both insects and mammalian species, although the trans configuration remains equally toxic to insects but is 100 times less toxic to mammals.[1] No specific molecular structure is identified that would be essential for the insecticidal activity, as reflected by the large number of synthetic compounds with good activity. Along with the stereospecificity, this indicates that the overall shape of the molecule is essential for binding to the site of action and exerting its effect in invertebrates and mammals.[1]

94.3.1 Box 94-1 Pyrethrins and Pyrethroids Often Used as Insecticides in House and Garden and for Flea Control

94.3.1.1 Type I Compounds (No α-Cyano Group)

Pyrethrin I

Allethrin

Bifenthrin

Bromophenothrin

Cismethrin

Kadethrin

Permethrin

Phenothrin

Resmethrin

Sumethrin

Tetramethrin

94.3.1.2

Type II Compounds (α-Cyano Group)

Cyfluthrin

Cyhalothrin

Cypermethrin

Deltamethrin

Fenpropathrin

Fenvalerate

Flucythrinate

Fluorocyphenothrin

Fluvalinate

Pyrethrins and pyrethroids have been classified further, based on the signs they induce in rat toxicity studies[3] in which two distinct patterns occurred. The type I or T-syndrome (T is for tremor) is characterized by aggressive sparring, increased sensitivity to stimuli, fine tremors, prostration, and hyperthermia. The type II or CS-syndrome (CS is for choreoathetosis and salivation) is characterized by pawing and burrowing, salivation, coarse tremors progressing to choreoathetosis (e.g., jerky, uncontrolled, excessive movements), clonic seizures, abnormal hind limb locomotion, and hypothermia. The main structural difference between the two groups of pyrethroids is the presence of an α-cyano group in the alcohol moiety of type II compounds (see Box 94-1). The two groups have slightly differing mechanisms of toxicity that manifest as distinct syndromes (see following section). The presence of the cyano group generally enhances toxicity of the pyrethroids in both mammals and insects.[1]

94.4

TOXICOKINETICS AND METABOLISM

Toxicokinetic data are scarce and are based largely on findings in rodents. This should be kept in mind when applying these results to dogs and cats. Furthermore, there are significant differences between compounds and isomers, altogether painting a heterogeneous toxicokinetic picture. Pyrethrins and pyrethroids are rapidly and extensively absorbed from the gastrointestinal (GI) tract after oral administration. Peak serum concentrations may be reached after 2 to 4 hours. A corn oil vehicle decreased the LD_{50} for various substances (including permethrin) in acute toxicity trials in rats.[1] Dermal absorption is significantly lower, less than 2%, but is greatly enhanced if applied in an emulsion (as compared with a dust formulation).[1,4] Grooming, and thus oral ingestion of the toxin, may significantly increase the bioavailability. Inhaled pyrethroids are absorbed effectively from the respiratory tract. The lipophilicity of the pyrethroids allows for a large volume of distribution and easy penetration of the blood-brain barrier. Although preferential distribution to fat tissue was similar for all pyrethroids, its extent varied among various compounds and stereoisomers.[1] The oral or intravenous dose administered and brain tissue concentration reached correlate well with the degree of toxicity, but the same is not true for blood levels.[1] The plasma elimination half-life after a single oral or intravenous dose of permethrin has been determined to range from 8 to 17 hours in rats, but is significantly longer in neural tissue.[5] Also, the maximum nervous tissue permethrin concentration was higher than that plasma, indicating accumulation in these tissues.[5] Different isomers may have different elimination half-times; the trans isomer of permethrin was eliminated 10 times faster than the cis isomer in a person following intentional pyrethroid ingestion.[6]

Biotransformation of pyrethrins and pyrethroids consists of hydrolysis by tissue and plasma esterases at the central ester bond and oxidation by hepatic mixed function oxidases at various sites in the acid or alcohol moiety. The latter mechanism may be enhanced with long-term exposure by induction of microsomal enzymes,[7] and their upregulation is also a mechanism of pyrethroid resistance in insects.[8] All metabolites lack gross activity and are 395 excreted renally after hydroxylation or conjugation to glycine, glucuronides, glucosides, or sulfates.[1] The ability for 396 efficient metabolic inactivation is an important factor for limiting acute neurotoxicity. Synergists, substances that are commonly added to pyrethroids to enhance their insecticidal potency and duration of action, exert their effect by inhibiting esterases and P-450–dependent monooxygenases. These compounds, such as piperonyl butoxide, N-octyl bicycloheptene dicarboximide (MGK 264), sulfoxide, sesamin, and sesamolin, may increase mammalian neurotoxicity of pyrethroids, carbamates, and organophosphates.[2] Inefficient glucuronide conjugation in the feline liver leads to an accumulation of phase I metabolites. This, in turn, slows primary hydrolysis and oxidation of the parent compound, and thus decelerates detoxification. However, toxicokinetic data for the cat that would further substantiate and detail this assumption are lacking.

94.5 MECHANISM OF TOXICITY

The vast majority of the toxic effects of pyrethrins and pyrethroids are a consequence of their mode of action on the central and peripheral nervous systems and the associated impact this has on other organ systems. The neurotoxicity of pyrethroids has been reviewed.[1,8] The main mechanism of action in both insects and mammals is its reversible interplay with voltage-sensitive sodium channels (VSSCs), leading to a disruption of their function. Pyrethroids slow both the activation or opening and the inactivation or closure of the VSSCs. Furthermore, the threshold potential at which these channels open is shifted toward a more negative value, thus allowing earlier cell membrane depolarization. Type I pyrethroids open the VSSCs only long enough to cause repetitive firing of action potentials, although type II compounds hold the channels open for much longer, thereby leading to extended depolarization and depolarization-dependent block. This is hypothesized to be the mechanistic basis for the distinctive T-syndrome and CS-syndrome that were previously discussed.[9] In addition, stereospecificity markedly influences affinity of pyrethroids to their binding site on the VSSCs and thus the potency of the compound. Importantly, there are different forms of VSSCs, with different sensitivities to pyrethroids, different functional roles, and different distribution patterns to regions of the nervous system, all of which contribute to the neurotoxic picture.[9]

Little is known about the distribution of various sodium channel subtypes within the nervous system. Electroencephalographic and neurochemical data from rats suggest that neuroexcitatory effects of pyrethroid intoxication manifest throughout the central nervous system, but may favor the cerebellum.[1] Hyperexcitability in peripheral sensory nerves was documented in electrophysiologic experiments in rats and may explain the clinically observed paresthesia.[1]

To complicate things further, pyrethroids were also shown to interact with other channels and receptors. Type II pyrethroids antagonize peripheral and central γ-aminobutyric acid receptors, thus facilitating excitatory neurotransmission.[1,2] The seizure activity seen with type II toxicity (CS-syndrome) may be a consequence.[8] Evidence suggests that the interaction of pyrethroids on voltage-dependent chloride and calcium channels may also contribute to its neurotoxicity.[8]

Insects are three orders of magnitude more sensitive to the toxic effects of pyrethrins and pyrethroids than mammals, and several explanations for this are possible. The most important factor is the increased sensitivity of insect sodium channels to pyrethroids, independent of body temperature.[10] Additionally, low body temperature, such as that of insects, increases the depolarizing effect of pyrethroids on VSSG, thus further enhancing the neurotoxic effect. Enzymatic removal of the active compound is also higher with elevated temperature. Whether a temperature-independent metabolic elimination of pyrethroids in insects is responsible for selective toxicity, as traditionally accepted, has not been proven.[10] Finally, the smaller body size of the insects leads to quick diffusion to the target site and leaves little time for enzymatic detoxification. Cumulatively, these factors result in a selectivity ratio of up to several thousand (Table 94-1).[10]

Metabolic variations among mammalian species can significantly alter susceptibility to overt intoxication. This may be the cause for the strikingly different sensitivities of dogs and cats to pyrethrins and pyrethroids.

94.6 CLINICAL PRESENTATION AND DIAGNOSIS

The diagnosis of pyrethrin or pyrethroid toxicity is based on exposure history, clinical findings, and exclusion of differential diagnoses.

Most animals, particularly cats and small dogs, will have a history of recent dermal application of an insecticide. In a retrospective study evaluating 116 cats with pyrethrin or pyrethroid toxicity, more than 90% developed toxicity after dermal application.[11] Severe signs are most often seen after administration of highly concentrated (45% to 65%) permethrin spot-on products labeled for dogs only, that are intentionally or accidentally administered to cats. Even close contact with a recently treated dog may be sufficient to induce convulsions in a cat. However, severe intoxications in cats have also occurred following the use of spot-ons labeled for this species (sumethrin). Clinical signs of toxicity typically become apparent within a few minutes to hours, but may be delayed up to 72 hours.[4,11,12]

In mild to moderately affected cats, symptoms include hypersalivation, mild tremors, hyperexcitability or depression, and GI signs like vomiting (especially when ingested) and diarrhea. Ear twitching, paw licking, repeated contractions of the superficial cutaneous musculature, rolling on the floor and rubbing the back (as observed in cats), may all indicate paresthesia, which is typically limited to the directly exposed skin area.[1] In more severely affected cats, disorientation, hyperthermia, and muscle fasciculations, generalized tremors, or seizures may occur.[12] Distinct differences between syndromes exhibited after type I (e.g., permethrin) versus type II (e.g., fenvalerate) pyrethroids have not been described in cats,[11] but most intoxications occur with type I compounds, rendering systematic comparison difficult.

No specific findings are expected on blood work other than those reflecting a secondary physiologic response to stress and tremors or seizures, such as hyperlactatemia and hyperglycemia,[1,2] but clinical pathologic information may be of significant importance to guide symptomatic treatment.

Although not many veterinary laboratories determine pyrethrin and pyrethroid levels on blood or tissue samples, it is possible to screen for a number of substances such as pyrethrins, allethrin, bifenthrin, cyfluthrin, cypermethrin, fenvalerate, and permethrin. However, it is not possible to relate the absolute concentration of insecticide in blood 396
or tissues with the severity of symptoms or intoxication, because the LD_{50} values for dogs and cats have not been 397
determined. Therefore the presence of pyrethrin or pyrethroid compounds in blood or tissues serves only to indicate exposure to the respective insecticide. Thus historical, clinical, and possibly postmortem findings remain essential for making an accurate diagnosis.

Table 94-1 Stepwise Analysis of Variables Contributing to Selective Toxicity of Pyrethroids

Selectivity Factor	Mammals	Insects	Difference
Potency on Nerve			
Due to temperature	Low (37° C)	High (25° C)	5
Due to intrinsic sensitivity	Low	High	10
Recovery	Fast	Slow	5
Detoxification Rate			
Due to enzymatic action	High	Slow	3
Due to body size	High	Low	3
Overall difference	—	5 × 10 × 5 × 3 × 3 =	2250

Modified from Narahashi T: Neuroreceptors and ion channels as the basis for drug action: past, present, and future. *J Pharmacol Exp Ther* 294:1, 2000.

94.6.1

Box 94-2 Toxins Causing Tremors or Seizures

- Anticholinesterase insecticides
- Organophosphates
- Carbamates
- Diethyltoluamide (DEET)
- Metaldehyde
- Organochlorines

- Dichlorodiphenyltrichloroethane (DDT)
- Bromethalin
- Strychnine
- Zinc phosphide
- Avermectin and ivermectin
- Tremorgenic mycotoxins
- Penitrem A, roquefortine
- Cocaine
- Amphetamines
- Methylxanthines
- Mushrooms

If there is no history of exposure to pyrethrins and pyrethroids, other tremor-inducing or seizure-inducing toxins should be considered (Box 94-2) and respective analysis may be of diagnostic value (e.g., determination of whole blood cholinesterase activity).

94.7 TREATMENT

Therapeutic measures consist of decontamination combined with supportive measures based on the clinical abnormalities displayed by the patient.

Following dermal exposure, decontamination consists of bathing the patient with copious amounts of warm water. Excessively high water temperatures may increase cutaneous blood flow and subsequent dermal absorption of the toxin and should therefore be avoided. In contrast, low water temperatures may lead to hypothermia and exacerbation of symptoms such as tremors. The additional use of a mild liquid dish detergent or noninsecticide shampoo will facilitate removal of the lipophilic toxin and its solvent, respectively.

In animals with oral ingestion, the general guidelines for GI decontamination apply (see Chapter 77, Approach to Poisoning and Drug Overdose). Some pyrethroids undergo enterohepatic circulation, so repeated administration of activated charcoal may hasten elimination of the toxin.[2] Oral exposure to pyrethrins or pyrethroids may cause abnormal mucosal sensations (paresthesia) leading to hypersalivation, lip smacking, and frothing. Offering small amounts of a highly palatable food may lessen these signs.[4]

Nonclinical investigations have looked at the treatment of systemic poisonings using various ion-channel or membrane-stabilizing drugs, including local anesthetics (lidocaine), phenytoin, phenobarbital, pentobarbital, valproic acid, diazepam, urethane, ivermectin, mephenesin, and its longer acting derivative, methocarbamol.[8,13] These substances have not undergone systematic clinical evaluation for efficacy and safety in human or veterinary medicine. Thus pharmaceutical recommendations rely largely on empiric data and typically include a combination of atropine, diazepam, barbiturates, and methocarbamol.[4,12-14]

Animals with severe ptyalism may benefit from a low dose of atropine (0.02 to 0.04 mg/kg IV, IM or SC) which may decrease cholinergically mediated hypersalivation caused by pyrethroids.[14] In contrast, hypersalivation due to anticholinesterase insecticide intoxication is typically not controlled with low-dose atropine therapy, and a lack of response may therefore suggest organophosphate or carbamate toxicity.[14]

Although the γ-aminobutyric acid receptor is unlikely to play a major role in pyrethrin and pyrethroid intoxications,[1] there is experimental evidence that administration of diazepam and barbiturates may delay the onset of neurotoxicity and decrease mortality.[15] The use of diazepam (0.25 to 1.0 mg/kg IV titrated to effect) in severely affected animals with seizure activity or phenobarbital (4 to 16 mg/kg IV titrated to effect) in cases unresponsive to benzodiazepines is not debated. The adverse cardiopulmonary effects of these substances should be taken into consideration (see Chapter 185, Anticonvulsants). Lower, nonanesthetic dosages of these two substances (diazepam 0.1 to 0.25 mg/kg IV; phenobarbital 2 to 4 mg/kg IV) may be used in animals that are not seizing but continue to have significant tremors despite methocarbamol therapy.[4,13,14]

Methocarbamol is a centrally acting muscle relaxant that is structurally related to guaifenesin. Its exact mechanism of action is not well understood. Methocarbamol administration is recommended at 44 to 220 mg/kg IV for control of pyrethroid-induced tremors. The dosage is generally chosen according to the severity of signs.[12] However, it is prudent not to exceed the maximal rate of administration suggested in humans (5 mg/kg/min) in order to prevent significant hypotension. The undiluted solution is hypertonic and may cause thrombophlebitis, especially if extravasated, so dilution with 0.9% saline or 5% dextrose in water is recommended. The initial dose of methocarbamol may be repeated, as clinically indicated, every 6 to 8 hours, although a total of 330 mg/kg q24h should not be exceeded. Methocarbamol alone will often not abolish the tremors completely, and the sedative effect of methocarbamol may exacerbate CNS depression when additional drugs, such as diazepam and barbiturates, are required.

In addition to controlling seizures and tremors, it is of paramount importance to identify abnormalities such as dehydration, hyperthermia, cranial nerve deficits, and cardiovascular impairment. Therefore a thorough physical examination is essential, and initial blood work will enable recognition of electrolyte, acid-base, and metabolic abnormalities (e.g., hypocalcemia, lactic acidosis, or hypoglycemia). Supportive treatment should be provided accordingly. Animals with significant changes in their vital parameters (e.g., hypotension) should be stabilized before decontamination. Hyperthermia is typically self-limiting once the tremors have been controlled and intravenous fluids administered. Care should be taken to avoid inducing hypothermia, which may increase the toxicity of pyrethroids and prolong recovery.

94.8 PROGNOSIS

Dogs and cats generally have an excellent prognosis after exposure to pyrethrins and pyrethroids, as long as appropriate medical attention is provided.[4,16] Most cats that receive supportive treatment will be well enough for discharge within 24 to 96 hour of presentation, unless severe systemic illness or secondary brain injury evolve as sequelae to prolonged seizure activity or hyperthermia.[4,16] Fatal outcomes may occur in cats following contact with highly concentrated pyrethroids labeled for use in dogs only, or in patients in which treatment and supportive care are withheld.

94.9 Suggested Further Reading*

DM Soderlund, JM Clark, LP Sheets, et al.: Mechanisms of pyrethroid neurotoxicity: Implications for cumulative risk assessment. *Toxicology*. **171**, 2002, 3, *Most complete review of all aspects relevant to the toxic effects of pyrethroids, with a detailed presentation of data describing mechanism of toxicity*.

PA Volmer: Pyrethrins and pyrethroids. In KH Plumlee (Ed.): *Clinical veterinary toxicology*. 2004, Mosby, St Louis, *Short and comprehensive review of the topic with a focus on clinical veterinary medicine*.

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* See the CD-ROM for a complete list of references

95 Chapter 95 Snake Envenomation

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95.1 KEY POINTS

- Severity of the envenomation depends on the species of snake, nature and location of the bite, and the size of the victim.
- Snake envenomation can be unpredictable and can progress, necessitating continuous monitoring and reassessment.
- Antivenin therapy is the only proven treatment that will improve the outcome of moderate to severe pit viper envenomations.
- Continued progression of clinical signs or failure of clinical signs to improve may be an indication for repeated antivenin therapy.
- Coral snake envenomation causes flaccid paralysis with little or no local tissue reaction.

95.2 PIT VIPER ENVENOMATION

Pit vipers are the largest group of venomous snakes in the United States and are involved in an estimated 150,000 bites annually of dogs and cats. In North America members of the family Crotalidae belong to three genera: the rattlesnakes (*Crotalus* and *Sistrurus* spp) and the copperheads and cottonmouth water moccasins (*Agkistrodon* spp).

Agkistrodon species, the copperheads and water moccasins, are found throughout the eastern and central United States. Copperheads are responsible for most venomous snakebites to humans in North America because of their proclivity for living next to human habitation. Water moccasins can be pugnacious and have a greater tendency to deliver venom when they bite. Rattlesnakes (*Crotalus* and *Sistrurus* spp) are found throughout the continental United States and account for most deaths in both human and animal victims. Clinicians should become familiar with their regional indigenous poisonous snake species.

The venom is not considered more toxic during the summer months; however, snakes show increased aggression and venom yield with environmental warming and longer photoperiod (as in the spring and summer). The maximum venom yields occur during the hottest months of summer.

Pit vipers control the amount of venom they inject during a bite. The amount injected depends on the snake's perception of the situation. Initial defensive strikes often are not envenomating. Offensive bites meter a given amount of venom into the victim, and agonal bites deliver the entire venom load and are therefore the most dangerous.

The severity of any pit viper bite is related to the volume and toxicity of the venom injected as well as to the location of the bite, which may influence the rate of venom uptake. As a generalization, the toxicity of pit viper venoms ranges in descending order from the rattlesnakes to the water moccasins and then to the copperheads. The toxicity of rattlesnake venom varies widely. Of the rattlesnakes, 9 species and 12 subspecies have populations with venoms containing proteins that are immunologically similar to the potent neurotoxic Mojave toxin. It is possible for pit viper venom to be strictly neurotoxic with virtually no local signs.

Pit viper venoms are a complex combination of enzymatic and nonenzymatic proteins. The primary purpose of the venom is not to kill but rather to immobilize the prey and predigest its tissues. The venom is 90% water and has a minimum of 10 enzymes and 3 to 12 nonenzymatic proteins and peptides in any individual snake.

The envenomation syndrome reflects the complexity of the venom. The body has to respond to the effects of multiple venom fractions, metabolize each, and cope with the resultant myriad of metabolites. In addition to the individual pharmacologic properties of these proteins and their metabolites, it has been demonstrated that some components act synergistically in producing specific effects or reactions. The net effect of this interaction of venom with the victim's response is a metabolic stew of toxic peptides and digestive enzymes. Additionally, the traditional categorization of pit vipers as having only hematoxic venoms should be reevaluated because some subpopulations of rattlesnakes possess only neurotoxic venom.

The onset of clinical signs after a snakebite may be delayed for several hours. Forty percent of all severe envenomations in humans are graded as mild to without envenomation sometime during the syndrome. In humans it is estimated that 20% of all pit viper bites are without envenomation (i.e., dry), with an additional 25% classified as mild.

Every pit viper envenomation is different. The victim affects the severity of an envenomation by such factors as species of victim, body mass, location of bite, post-bite excitability, and use of premedications (e.g., nonsteroidal antiinflammatory drugs in older dogs that may make the victim more susceptible to clotting defects). The snake affects the severity of the envenomation by species and size of snake, age of snake, motivation of snake, and degree of venom regeneration since last use.

Cats are more resistant, on the basis of milligram of venom per kilogram of body mass, to pit viper venom than dogs. However, cats generally arrive for veterinary care in a more advanced clinical condition. This is probably due to the cat's smaller body size and the proclivity of cats to play with the snake, thereby antagonizing it and inducing an offensive strike, often to the torso. Additionally, cats commonly run off and hide after being bitten before they return home, thus delaying the time from bite to veterinary care. Because dogs generally receive more defensive strikes, have a larger body mass, and more frequently seek immediate human companionship after injury, they are more likely to receive medical attention promptly.

95.2.1 Clinical Signs

It is possible that a life-threatening envenomation may occur with no local clinical signs other than the puncture wounds themselves. Local tissue signs of pit viper envenomation include puncture wounds, one to six from a single bite, which may be bleeding. Rapid onset of pain may ensue with progressive edema. Ecchymosis and petechiation may manifest. Tissue necrosis may occur, particularly in envenomations to areas without a significant subcutaneous tissue mass. The presence of fang marks does not indicate that envenomation has occurred, only that a bite has taken place. It must be reiterated that the severity of local signs does not necessarily reflect the severity of the systemic envenomation.

Systemic clinical manifestations encompass a wide variety of problems, including pain, weakness, dizziness, nausea, severe hypotension, thrombocytopenia, fasciculations, regional lymphadenopathy, alterations in respiratory rate, increased clotting times, decreased hemoglobin concentration, abnormal electrocardiogram findings, increased salivation, echinocytosis of red blood cells, cyanosis, proteinuria, bleeding (e.g., melena, hematuria, hematemesis), obtundation, and convulsions. Not all of these clinical manifestations are seen in each patient, and they are listed in descending order of frequency as seen in human victims.

Severe hypotension results from pooling of blood within the “shock organ” of the species bitten (i.e., the hepatosplanchnic [dogs] or pulmonary [cats] vascular bed) in addition to fluid loss from the vascular compartment secondary to severe peripheral swelling. This swelling can be significant.

The victim's clotting anomalies largely depend on the species of snake involved. Coagulopathies range from direct blockage or inactivation of various factors in the patient's clotting cascade to the possible destruction of megakaryocytes in the circulating blood and bone marrow. Approximately 60% of envenomated patients develop a coagulopathy, by far the most common being hypofibrinogenemia with prolonged clotting times. Venom-induced thrombocytopenia occurs in approximately 30% of envenomations, with an unmanaged nadir usually occurring between 72 and 96 hours. Syndromes resembling disseminated intravascular coagulation are possible with pit viper envenomations.

Myokymia, a type of fasciculation of various muscle groups, frequently is reported in humans after bites received by timber rattlesnakes *(Crotalus horridus horridus)* and western diamondback rattlesnakes *(Crotalus atrox)*. [1]

95.2.2

Monitoring

Monitoring of the severity and progression of the clinical envenomation syndrome may be difficult. A tool that has proven useful is the envenomation severity scoring system (Box 95-1). Use of this system more accurately quantifies the severity of the patient's condition over time and allows a more objective assessment than is usual without it.[2] It is recommended that a severity score be acquired upon entry and 6 hours, 12 hours, and 24 hours after admission.

A complete blood count with differential, including platelet count, should be obtained; red blood cell morphology along with baseline serum chemistry with electrolytes should be performed. A coagulation profile should be obtained including activated clotting time, prothrombin time, partial thromboplastin time, fibrinogen level, and fibrin degradation products. Urinalysis with macroscopic and microscopic evaluations including free protein and hemoglobin-myoglobin should be performed. An electrocardiogram may be indicated in animals with significant envenomations. These laboratory tests should be repeated periodically to monitor the progression of the syndrome and the effectiveness of therapy.

Circumferential measurements of the affected body part at, above, and below the bite site at set intervals aid in objective monitoring of the progression of the swelling secondary to many pit viper bites. Transient (within 48 hours) echinocytosis has been reported in dogs, and its presence is an indicator of envenomation. However, absence of this morphologic change is not an indicator of lack of envenomation.

Hypokalemia has been reported subsequent to pit viper envenomations. In one series potassium levels of less than 3.5 mEq/L were observed in 11% of 97 pit viper–envenomated dogs. It is postulated that this decrease is secondary to the release of epinephrine by the patient, inducing serum insulin elevation and thereby driving potassium into the cells. This is a transient phenomenon that corrects with intravenous fluid and antivenin administration.

95.2.3

Treatment

Although many first aid measures have been advocated for pit viper bite victims, none has been shown to prevent morbidity or mortality.

First aid measures to be avoided include ice, incision and suction, tourniquets (which constriction bands quickly become with progressive limb swelling), and hot packs. Electroshock has been shown definitively to be ineffective for pit viper envenomations and should not be attempted.[3] Recommendations for first aid in the field are to keep the victim calm, keep the bite site below heart level if possible, and transport the victim to a veterinary medical facility for primary medical intervention.

The patient should be hospitalized and monitored closely for a minimum of 8 hours for signs of envenomation. A severity score sheet should be recorded upon entry and at 6 hours after hospitalization at a minimum for every suspected snakebite victim. The effects of snake venom are time dependent; any delay in initiating medical treatment is deleterious to the patient and may result in complications that cannot be corrected.

The initial medical response to a snake-bitten patient is to collect the appropriate pretreatment laboratory samples and make circumferential measurements at, above, and below the bite site to allow quantitative monitoring of the progression of swelling. An intravenous catheter should be placed and a crystalloid fluid drip started.

The patient can be pretreated with diphenhydramine given intravenously or subcutaneously (small dogs and cats: 10 mg; large dog: 25 to 50 mg). Antihistamines have no effect on the venom or the course of the envenomation itself; however, they can calm the fractious patient to facilitate intravenous catheterization and minimize possible allergic reactions to antivenin.

95.2.4

Antivenin

The only proven therapy specific of pit viper envenomation is antivenin. Coagulation deficits, fluid loss, changes in neurologic status, cardiac conduction abnormalities, and the necrotizing effect of the venom can be reversed dramatically when antivenin treatment is initiated appropriately.

95.2.4.1

Box 95-1 Snake Bite Severity Score

Score	Severity
Pulmonary System	
0	Signs within normal limits
1	Minimal: Slight dyspnea
2	Moderate: Respiratory compromise, tachypnea, use of accessory muscles
3	Severe: Cyanosis, air hunger, extreme tachypnea, respiratory insufficiency, or respiratory arrest from any cause
Cardiovascular System	
0	Signs within normal limits
1	Minimal: Tachycardia, general weakness, benign arrhythmia, hypertension
2	Moderate: Tachycardia, hypotension (but tarsal pulse still palpable)
3	Severe: Extreme tachycardia, hypotension (nonpalpable tarsal pulse or systolic blood pressure <80 mm Hg), malignant arrhythmia, or cardiac arrest
Local Wound	
0	Signs within normal limits
1	Minimal: Pain, swelling, ecchymosis, erythema limited to bite site
2	Moderate: Pain, swelling, ecchymosis, erythema involves less than half of extremity and may be spreading slowly
3	Severe: Pain, swelling, ecchymosis, erythema involves most or all of one extremity and is spreading rapidly
4	Very severe: Pain, swelling, ecchymosis, erythema extends beyond affected extremity, or significant tissue slough
Gastrointestinal System	
0	Signs within normal limits
1	Minimal: Abdominal pain, tenesmus
2	Moderate: Vomiting, diarrhea
3	Severe: Repetitive vomiting, diarrhea, or hematemesis
Hematologic System	
0	Signs within normal limits
1	Minimal: Coagulation parameters slightly abnormal, PT <20 sec, PTT <50 sec, platelets 100,000 to 150,000/mm^3
2	Moderate: Coagulation parameters abnormal, PT 20 to 50 sec, PTT 50 to 75 sec, platelets 50,000 to 100,000/mm^3

3	Severe: Coagulation parameters abnormal, PT 50 to 100 sec, PTT 75 to 100 sec, platelets 20,000 to 50,000/mm^3
4	Very severe: Coagulation parameters markedly abnormal with bleeding present or the threat of spontaneous bleeding, including PT unmeasurable, PTT unmeasurable, platelets <20,000/mm^3
Central Nervous System	
0	Signs within normal limits
1	Minimal: Apprehension
2	Moderate: Chills, weakness, faintness, ataxia
3	Severe: Lethargy, seizures, coma
Score	
0 to 20	Total score: 20 possible points Interpretation: <2 minimal severity 2 to 3 moderate severity 4 to 8 more severe >8 very severe

PT, Prothrombin time; *PTT,* partial thromboplastin time.

In North America polyvalent antivenin, which is effective against the venoms of all endemic pit viper species, is used. This polyvalent equine-origin antivenin *(Crotalidae)* is made and marketed to the veterinary community by Fort Dodge Laboratories (Fort Dodge, IA). The antivenin is produced by inoculating horses with the venoms collected from *C. atrox* (western diamondback rattlesnake), *Crotalus adamanteus* (eastern diamondback rattlesnake), *Crotalus terrificus* (South American rattlesnake), and *Bothrops atrox* (fer-de-lance). The processes used to extract these proteins result in a final product that, although rich in antibodies, is very high in equine protein contaminants and albumin, often in the range of 50%. These proteins are primarily responsible for the allergic reactions that can be associated with its use.

Skin testing for allergic reactions to the horse serum is difficult to evaluate in veterinary patients, and a test dose is not provided in the Fort Dodge Laboratories packaging. Generally, slow administration of the antivenin initially will identify those patients who may have an allergic reaction.

Antivenin should be reconstituted with the provided diluent; saline may be added to fill the vial completely, ensuring that the antivenin is totally submerged to speed reconstitution. It should not be shaken but can be swirled to facilitate reconstitution. This usually takes between 10 and 15 minutes. Warming the vial to body temperature aids in dissolution into the liquid state. Shaking or overheating can destroy the proteins and causes foaming, which makes it difficult to collect in a syringe.

Antivenin should be diluted at a ratio of one vial to 100 to 250 ml of crystalloid fluids. In smaller patients the clinician should adjust the infusion volume to prevent fluid overload. Administration should begin slowly as an intravenous infusion. If there is no evidence of an allergic reaction (e.g., nausea, hyperemia of inner pinna, fluffing of tail, pruritus), the rate of infusion can be increased. The entire initial dose should be given within a half hour. The patient then should be reevaluated for further progression of the envenomation syndrome using the appropriate clinical and laboratory parameters.

The dosage of antivenin is calculated relative to the amount of venom injected, the body mass of the victim, and the bite site. Bites to the torso, tongue, or intravascular areas are severe envenomations that require prompt, aggressive antivenin administration. Smaller patients require higher doses because the dose of venom per kilogram of body weight of the victim is higher. Multiple vials may be necessary to manage severe envenomations adequately. The average dosage in dogs and cats is one to two vials of antivenin.

The earlier antivenin is administered, the more effective it is. The package insert advises using it within the first 4 hours. However, the product is effective as long as active venom components are found in the bloodstream. Tissue necrosis will not be reversed once it has occurred, but additional damage may be prevented.

Antivenin is extremely effective in reversing venom-induced coagulation defects. Coagulation defects can be abated several days after envenomation. If clotting defects continue to manifest, additional antivenin should be administered. Disseminated intravascular coagulation–like syndromes should be managed with additional antivenin. Rattlesnake venom thrombin-like enzymes are not inhibited by heparin, and it should not be administered. Clotting anomalies secondary to envenomations are extremely difficult to reverse with blood products and transfusions.

Antivenin is extremely effective in reversing most rattlesnake venom–induced thrombocytopenias. However, in timber rattlesnake *(Crotalus horridus)* bites a platelet aggregating protein induces thrombocytopenia that is resistant to antivenin even though prothrombin time and partial thromboplastin time are restored.

Patients exhibiting allergic reactions to antivenin can still receive it if needed in severe envenomations. It can be given as a slow intravenous drip and piggybacked with diphenhydramine and possibly epinephrine. Data in both human envenomation and veterinary envenomation databases have not identified a significantly higher reaction rate in patients who have received antivenin previously. Some veterinary patients have received antivenin yearly for several consecutive years.

Allergic reactions, although rare, are possible when administering antivenin. These can become manifest in one of three ways: by true anaphylaxis, an anaphylactoid reaction, and delayed serum sickness. The most common reaction to antivenin is an anaphylactoid reaction. This is a complement-mediated reaction to the rapid administration of a foreign protein, such as those seen in rapidly administered blood transfusions. Anaphylactoid reactions usually can be managed by stopping the antivenin infusion, administering diphenhydramine intravenously (small dogs and cats: 10 mg; large dogs: 25 to 50 mg), waiting 5 minutes, and then restarting the infusion at a slower rate.

Anaphylaxis is managed by stopping the infusion of antivenin and administering epinephrine, glucocorticoids, and crystalloid fluids. Patients receiving β-blockers must be monitored very closely. β-Blockers may mask the early onset of anaphylaxis, which becomes more difficult to reverse as the reaction progresses. Delayed serum sickness is rare in dogs and cats. This may be due to the smaller volumes of antivenin administered relative to those given to human patients. Onset of delayed serum sickness usually occurs 7 to 14 days after antivenin administration. If it does occur, management consists of antihistamines, often type 1 and type 2 inhibitors, or glucocorticoids, or both.

A new antivenin (*Crotalidae* polyvalent immune Fab Ovine, Protherics, Brentwood, TN) was approved for the human use by the U.S. Food and Drug Administration in late 2000. The new antivenin is a purified and lyophilized preparation of ovine Fab immunoglobin fragments. The ovine IgG molecules are cleaved to discard the inflammation-stimulating Fc portion of the antibody, retaining only the Fab molecules. The product is affinity purified and contains negligible amounts of extraneous proteins such as albumin.

Crotalidae polyvalent immune Fab (ovine) antivenin is prepared from the blood of healthy sheep immunized in groups with one of the following North American crotalid venoms: *C. atrox* (western diamondback rattlesnake), *Crotalus adamanteus* (eastern diamondback rattlesnake), *Crotalus scutulatus scutulatus* (Mojave rattlesnake), and *Agkistrodon piscivorus* (cottonmouth or water moccasin). A monospecific antivenin is produced from each sheep group, and these four monospecific antivenins are then mixed to prepare the final polyvalent product. This antivenin has been used successfully in many dogs and cats.

If the patient is in severe hypovolemic shock, volume expansion with isotonic crystalloids or colloids is indicated. Hemoglobin glutamer-200 (bovine; Oxyglobin, Biopure, Cambridge, MA) may be administered as a colloid volume replacer and to increase oxygen delivery to damaged tissues. Oxyglobin has an advantage over other colloids in that it does not run the risk of inducing additional clotting abnormalities in the patient. There is debate about the use of colloidal fluids in pit viper–envenomated patients, because leakage of the colloid through damaged vascular walls may pull fluid out of the vascular space and into areas with rich capillary beds such as the pulmonary tissues.

Broad-spectrum antibiotics are recommended in veterinary patients after envenomation because of the number of pathogenic bacteria found in snakes' mouths and the amount of local tissue damage at the bite site.

Pain usually is controlled with the antivenin. However, in patients in which no or limited amounts of antivenin are administered, pain control may require intravenous opioids during the first 24 hours. Fentanyl is preferred and can be administered as a contstant rate infusion (loading dose 2 μg/kg, then 0.5 μg/kg/hr). Morphine should be avoided because of its histamine-releasing activity, which may be confused with the onset of anaphylaxis. Nonsteroidal medications compound the risk of blood dyscrasias and clotting anomalies.

Glucocorticoids are not recommended for managing pit viper envenomation. They have been advocated repeatedly, yet the rationale for their use is obscure and their ultimate therapeutic value is controversial. Numerous studies have examined the effects of treating venomous snakebites with glucocorticoids. Most report a worsening of or no improvement in the patient's condition.[4,5] Some studies have shown dramatic increases in 402
mortality. Human clinical trials have shown no beneficial effects from glucocorticoids. They are of little use in a 403
hypotensive crisis and have little if any effect on the local tissue response to pit viper venom.

Fasciotomy is not indicated in the dog and cat. The rationale for this procedure is to combat damage from compartment syndromes, which are extremely rare in dogs and cats and are not common in humans.

The differential diagnoses for snakebites includes trauma, angioedema (e.g., insect bites and stings), other animal bites, draining abscesses, and penetrating wounds.

95.3 CORAL SNAKE ENVENOMATION

Two genera of coral snakes are indigenous to the United States, composed of two species and three subspecies. One genus is *Micruroides. Micruroides euryxanthus,* the Sonoran coral snake, inhabits central and southeastern Arizona and southwestern New Mexico. The other genus is *Micrurus,* with three subspecies: *Micrurus fulvius fulvius* (eastern coral snake), *Micrurus fulvius tenere* (Texas coral snake), and *Micrurus fulvius barbouri* (South Florida coral snake).

The Texas coral snake has a home range extending from southern Arkansas and Louisiana throughout eastern and west central Texas. The eastern coral snake inhabits eastern North Carolina south to central Florida and west to Alabama, Mississippi, and eastern Louisiana to the Mississippi River. The South Florida coral snake is found in southern Florida and the northern Florida Keys.

North American coral snakes are distinctively colored, beginning with a black snout and an alternating pattern of black, yellow (occasionally white), and red. They can be differentiated from similar looking nonpoisonous snakes by the coral snake's color bands, which completely encircle the snake's body with the yellow band touching the red band. This color pattern can be best remembered by the warning that if caution (yellow) touches danger (red), the snake is a coral snake.

Bites by coral snakes are relatively rare. In humans, coral snakes account for less than 1% of all venomous snakebites in North America.

The Sonoran coral snake *(M. euryxanthus)* is a small burrowing snake that is relatively innocuous. There are no reported cases of dog or cat fatalities caused by envenomation by this snake.

The severity of a coral snakebite is related to the volume of venom injected and the size of the victim. Sixty percent of coral snakebites are not envenomating. The length of the snake correlates positively with the venom yield. Venom uptake can be delayed for many hours and can take 7 to 14 days to clear the body. One report involving envenomated cats described clinical improvement by 36 hours, and by 48 hours after the bite cats were moving their limbs.[5]

Coral snake venom is primarily neurotoxic with little local tissue reaction and pain at the bite site. Several neurotoxins may be involved and in combination act as nondepolarizing postsynaptic neuromuscular blocking agents. The net effect of the neurotoxins is a curare-like syndrome. Additionally, the venom induces central nervous system (CNS) depression, muscle paralysis, and vasomotor instability.

There have been reports of the venom causing hemolysis with severe anemia with marked hemoglobinuria.[6] The cause of the red blood cell destruction is poorly understood. It is speculated that it is due to the effects of phospholipase A and its interaction with red blood cell membranes.[6]

95.3.1 Clinical Signs

The onset of clinical signs may be delayed for as long as 10 to 18 hours.[6] The mean time from bite to onset of clinical signs in one human report was 170 minutes. There are few if any local signs other than the puncture wounds. Occasionally, local pain and regional paresthesia may occur. The victim then begins to have alterations in mental status and develops generalized weakness and muscle fasciculations. Progression to paralysis of the limbs and respiratory muscles then follows. These signs are consistent with bulbar dysfunction. The patient is at risk of impending respiratory failure, with pharyngeal spasms, hypersalivation, cyanosis, and trismus (spasms of the masticatory muscles). Aspiration pneumonia is the major complication secondary to marked salivation resulting from dysphagia.

Clinical signs of coral snake envenomation reported in dogs are acute CNS depression, emesis, excessive salivation, quadriplegia with decreased spinal reflexes in all limbs, and respiratory paralysis. Dogs may exhibit intravascular hemolysis, anemia, hemoglobinuria, and morphologic alterations of red blood cells. Hemolysis has occurred within 72 hours after envenomation.[6] Blood-tinged urine and diarrhea may be present.

Clinical signs of coral snake envenomation reported in cats are acute ascending flaccid quadriplegia, CNS depression, and impaired nociperception. Additionally, anisocoria, absent spinal reflexes in all four limbs, hypothermia, and loss of the cutaneous trunci reflex have been documented.[6] Anal tone and micturition are typically normal. Hemoglobinuria is not observed in cats. Hemolysis and hemoglobinuria were not evident in three clinical cases of envenomated cats.[6]

Baseline laboratory data should include a complete blood count, measurement of electrolytes, and serum chemistry analysis. Hyperfibrinogenemia and moderate leukocytosis are reported abnormalities. Creatinine kinase can be elevated significantly. Early elevation of creatinine kinase is an indicator that envenomation has occurred.[6] In dogs, red blood cell morphologic changes include burring and spherocytosis.[7] Canine patients in which coral snake envenomation is suspected should be monitored for progressing anemia and hemoglobinuria.

95.3.2 Treatment

The best field response to coral snake envenomation is rapid transport to a veterinary medical facility capable of 24-hour critical care and assisted ventilation. The following first aid measures should be avoided: incisions, ice, hot packs, or electroshock.

First aid advocated in Australia for *Elapid* bites is the immediate application of a compression bandage. This technique is obviously not applicable to bites of the neck and head. The compression bandage, such as an elastic or crepe bandage material, is applied rapidly to the bitten extremity, starting at the bite site and progressing to encompass the entire limb. The bandage should be wrapped as tightly as one would wrap a sprained ankle. This bandage should not be removed until primary therapy, specifically antivenin, is administered.

The victim should be hospitalized for a minimum of 48 hours for continuous monitoring. Of utmost importance is good supportive medical care along with an appreciation and anticipation of events that might develop. This includes care of a paralyzed patient and prevention of aspiration pneumonia. Fluid administration through an intravenous catheter should be given at a maintenance rate. Because the onset of clinical signs can be delayed for hours, extreme vigilance should be maintained in monitoring the patient.

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The only definitive treatment for coral snake envenomation is administration of antivenin *(M. fulvius)* that was made by Wyeth Laboratories (Marietta, PA). This antivenin was effective against the venom of all North American coral snakes except the Sonoran coral snake. However, Wyeth-Ayerst has discontinued production of this antivenin *(M. fulvius)*. There is no other approved coral snake antivenin available in the United States. Studies have shown protective cross-reactivity with either the Australian tiger snake *(Notechis scutatus)* or the Mexican coral snake *(Micrurus)*[8,9] antivenins in the mouse model. Other South and Central American coral snake antivenins do not protectively cross-react with venom of North American *Micrurus* spp.

The earlier that antivenin is administered the more effective it is. Once clinical signs of coral snake envenomation become manifest, they progress with alarming rapidity and are difficult to reverse. Antivenin is recommended in animals with clinical findings of one or more fang marks from which blood can be expressed or those with a history of the snake hanging by its mouth from the victim regardless of the absence of neurologic abnormalities.

Antivenin should be reconstituted with the provided diluent. It should not be shaken but can be swirled to facilitate reconstitution. This usually takes between 10 and 15 minutes. Warming the antivenin vial to body temperature aids in dissolution into the liquid state. Shaking or overheating can destroy the proteins and can cause excessive foaming, which makes it difficult to aspirate the antivenin into a syringe.

Antivenin should be diluted at a ratio of one vial to 100 to 250 ml of crystalloid fluids. In smaller patients the clinician should adjust the volume of fluid infused to prevent fluid overload. Administration should begin slowly as an intravenous infusion. If there is no evidence of an allergic reaction (e.g., nausea, hyperemia of the inner pinna, piloerection of tail hair, pruritus), the rate of infusion can be increased. The entire initial dosage should be given within a half hour. The patient must then be reevaluated for further progression of the envenomation syndrome using the appropriate clinical and laboratory parameters.

The dosage of antivenin is calculated relative to the amount of venom injected and the body mass of the victim. Smaller patients require higher doses of antivenin because the dosage of venom per kilogram body weight of the victim is higher. A single vial neutralizes 2 mg of coral snake venom. The recommended initial dosage is one to two vials of antivenin. Repeated doses are administered as indicated by the progression of the syndrome.[7] Multiple vials may be necessary to treat severe envenomations. The considerations and treatment of allergic reactions to pit viper antivenin can be applied to coral snake antivenin administration.

If antivenin is not available or if its administration is delayed, supportive care includes respiratory support. Assisted mechanical ventilation can be used and may have to be employed for up to 48 to 72 hours.[10]

Broad-spectrum antibiotics are recommended in the veterinary patient after envenomation, owing to the number of pathogenic bacteria found in snakes' mouths. The use of glucocorticoids to treat coral snake envenomation is not recommended, the justification for their use being tenuous at best. Treatment of Sonoran coral snake envenomation at this time is largely empiric because no specific antivenin is available. General supportive care and response to clinical manifestations are the mainstays of therapy.

Differential diagnoses include tick paralysis, botulism, acute polyneuritis, iatrogenic drug administration, polyradiculoneuritis, and myasthenia gravis.

95.4

SUGGESTED FURTHER READING*

C Chrisman, A Hopkins, S Ford, et al.: Acute, flaccid quadriplegia in three cats with suspected coral snake envenomation. *J Am Anim Hosp Assoc*. **32**, 1996, 343, *A case series of three cats with suspected coral snake envenomation in Florida, of which one cat received antivenin, and all three cats recovered in 7 to 10 days*.

S Marks, C Mannella, M Schaer: Coral snake envenomation in the dog: report of four cases and review of the literature. *J Am Anim Hosp Assoc*. **26**, 1990, 629, *In this report all dogs recovered in 1-3 weeks, one dog required mechanical ventilation due to respiratory paralysis*.

* See the CD-ROM for a complete list of references

96 Chapter 96 Spider Bite Envenomation

Michael E. Peterson, DVM, MS

96.1 KEY POINTS

- There are two genera of venomous spiders of clinical importance in North America, *Latrodectus* (black widow) and *Loxosceles* (brown recluse).
- Black widow spider bites induce no significant local symptoms but do cause acutely painful bites with muscle cramping, systemic hypertension, and possibly death.
- Cats are particularly sensitive to black widow spider venom, exhibiting extreme pain, vocalization, and muscle cramping, leading to flaccid paralysis and a high fatality rate.
- Black widow envenomations can be managed initially with pain management; however, antivenin is available and very efficacious.
- Brown recluse spider bites can cause one of two manifestations: an indolent dermatonecrotic ulcerative lesion or systemic hemolysis that can be life threatening.
- Brown recluse spiders are endemic only in certain parts of the United States, the diagnosis of brown recluse spider bite should be considered only in patients living in these regions.

96.2 BLACK WIDOW SPIDER ENVENOMATION

Five primary species that belong to the genus *Latrodectus* reside in the United States. These are *L. mactans, L. variolus, L. bishopi, L. hesperus,* and *L. geometricus. L. mactans* (the black widow) is the predominant species found throughout North America. These spiders are found throughout the continental United States and north into the southern Canadian provinces. They inhabit funnel-shaped webs in dry, dimly lit, secluded places. The web is irregularly shaped, has a tattered “cobwebbed” appearance, and usually is found in corners. The spiders commonly are found around houses where outside lights help to attract prey insects.

Male black widow spiders are of little medical importance, because they are unable to penetrate mammalian skin. The female can be identified by the hourglass pattern, red or orange in color, on the ventral aspect of her shiny, globose black abdomen. The hourglass becomes more prominent as the spider ages. It is important to recognize the immature female, which has a colorful pattern of red, brown, and beige on the dorsal surface of her abdomen, because she is fully capable of delivering a severe envenomation.

Black widow spiders control the amount of venom they inject using striated muscle. Therefore *Latrodectus* bites do not necessarily indicate envenomation. It is estimated that 15% of bites in humans are not envenomating. Cats are very sensitive to the venom, and deaths are common in envenomated victims. In the dog the toxin provokes severe symptoms, although dogs are considered more resistant than cats.[1] A single bite is fully capable of delivering a lethal dose of venom to companion animals. Evidence suggests that the venom has increased toxicity in spiders living in areas with higher environmental temperatures. Although some controversy exists, it appears that venom toxicity is highest in autumn and lowest in spring. The incidence of black widow spider bites in veterinary medicine is unknown. Diagnosis of *Latrodectus* envenomation in domestic animals rarely is made, primarily because of veterinary unfamiliarity with the clinical manifestations.

Black widow spider venom contains no locally acting toxins that would provoke a significant inflammatory reaction at the bite site. The venom contains a potent mammalian neurotoxin called *α-latrotoxin,* which induces neurotransmitter release from nerve terminals. This depolarization promotes calcium-independent release of the neurotransmitters acetylcholine and norepinephrine (and others) down concentration gradients and then inhibits their subsequent reuptake. Acetylcholine, noradrenaline, dopamine, glutamate, and enkephalin systems are all susceptible to the toxin.[2]

96.2.1 Clinical Signs

The onset of clinical signs usually occurs during the first 8 hours after envenomation. Local tissue changes are generally absent, and swelling at the bite site is uncommon. Systemic manifestations depend on two sets of variables. Spider-dependent variables include the size of the spider, motivation of the spider (e.g., quantity of venom it decides to inject), and time of year (e.g., altered venom toxicity). Victim-dependent variables would include species and size of victim, location of bite, underlying health problems, and age of the victim (e.g., pediatric and geriatric victims are more severely afflicted).

Initial regional numbness often is observed in dogs. Tenderness in adjacent lymph nodes may precede hyperesthesia, progressive muscle pain, and fasciculations in the affected region. Cramping of the muscles of the chest, abdomen, and lumbar and other large muscle masses is common. Abdominal rigidity without tenderness is a hallmark symptom of *Latrodectus* envenomation. The condition is extremely painful in moderate to severe envenomations. Significant respiratory distress may become evident if muscle cramping is strong. Marked restlessness, writhing, and muscular contortions may occur. Hypertension and tachycardia should be anticipated. In high-risk patients (i.e., those with underlying health problems or at either end of the age spectrum) these cardiovascular manifestations may lead to stroke, exacerbation of heart failure, and possibly myocardial ischemia. Signs of motor restlessness may abate over 10 to 20 hours with the possible onset of paralysis. Death is usually due to respiratory or cardiovascular collapse.

Cats are extremely susceptible to *Latrodectus* venom. In one study, 20 of 22 feline victims died subsequent to black widow envenomation; the average survival time after the bite was 115 hours.[1] Paralytic signs may appear early and are particularly marked. Severe pain is manifested by howling and loud vocalizations. Excessive salivation and restlessness are common, and vomiting and diarrhea may occur. Muscular tremors, cramping, ataxia, and inability to stand precede complete paralysis. The body becomes adynamic and atonic. A Cheyne-Stokes respiratory pattern may develop, and death ensues.

96.2.2 Treatment

First aid is essentially of no value in the treatment of *Latrodectus* envenomation. Patients presented for veterinary care usually are severely envenomated, because the diagnosis relies on signs. Therefore the incidence of “dry” and mild bites is inconsequential, and all diagnosed cases should be treated aggressively. The victim should be hospitalized for a minimum of 48 hours. The patient's vital signs should be measured frequently during the first 8 to 12 hours in the hospital. Hypertension is a significant threat. Serum chemistry analysis and a complete blood cell count should be obtained. No diagnostic test can confirm definitively that a black widow spider bite has occurred. Cats, however, often vomit the spider.

The primary treatment for black widow spider envenomation is administration of antivenin (*Latrodectus mactans* antivenin, equine origin; Merck & Co.). This antivenin is supplied in a lyophilized state and reconstitutes rapidly into 2 ml of supplied diluent. Antivenin should be administered by slow intravenous infusion. Allergic reactions can occur, and anaphylaxis is possible. Risk of allergic reactions may be decreased by diluting the antivenin into 100 ml of saline solution and administering over 30 minutes. Close monitoring of patients receiving β-blockers is important, because these compounds can mask the initial signs of anaphylaxis, which is more difficult to control as it progresses. The inner ear pinna should be monitored while the antivenin is administered. If hyperemia develops, the infusion is discontinued, and diphenhydramine (2 to 4 mg/kg SC) is administered. If the allergic manifestations abate, the antivenin infusion can then be restarted at a slower rate.

If the reaction recurs, the infusion is stopped, and consultation is sought. True anaphylactic reactions are rare. A human study of 2062 antivenin-treated patients reported anaphylactic reactions in only 11 recipients (0.54%), none of which was fatal. The veterinary clinician should be prepared to respond to an anaphylactic reaction by having the appropriate drugs, oxygen, and resuscitation equipment available before administering the antivenin. The most common reaction to the antivenin is a complement-mediated anaphylactoid type of reaction such as occurs with rapid infusion of a foreign protein (e.g., as with rapid blood transfusions). Indicated therapy should not be withheld because of fear of life-threatening reactions to the antivenin. The risks are low if antivenin is used properly. Antivenin treatment provides the most permanent and quickest relief of the envenomation syndrome, usually within 30 minutes of administration. One vial is usually sufficient, but a second vial may be indicated in severe envenomations. Delayed allergic reactions (serum sickness) are rare because of the low volume of foreign protein infused. The antivenin is not expensive, has a long shelf life, and can easily be stocked.

Extreme care should be taken with intravenous fluids. These patients are at high risk of developing hypertension as part of the envenomation syndrome. Benzodiazepines are more efficacious than muscle relaxants for black widow spider envenomation. Unlike the antivenin, these drugs do not correct the hypertension or respiratory distress often seen with this envenomation syndrome.

The prognosis of *Latrodectus* envenomation is uncertain for several days, and complete recovery may take weeks. In humans the average duration of the syndrome is 3 to 6 days. Untreated patients have exhibited signs for a period of 7 days, but weakness and some muscle pain and malaise may persist for weeks. Differential diagnoses include acute condition of the abdomen, intervertebral disk disease, and rabies (in cats).

96.3 BROWN RECLUSE SPIDER ENVENOMATION

There are 13 species of *Loxosceles* spiders resident in the United States. These spiders inhabit the south and south central states from Georgia through Texas and north to southern Wisconsin. Several other species live in the western United States. At least five species indigenous to the United States have been associated with necrotic arachnidism: *L. recluse* (the brown recluse), *L. refuscens, L. arizonica, L. unicolor,* and *L. laeta*.[3] They commonly are called *violin spiders* because of the violin-shaped marking on the dorsum of the cephalothorax, with the neck of the violin pointing toward the abdomen. Brown recluse bites are grossly overdiagnosed, usually in geographic regions where they do not exist. Clinicians should become aware of indigenous species of spiders.[3-5]

These animals are nocturnal and are generally active from spring through fall. They are obviously reclusive and live in dark, secluded locations such as areas with rocks and surface debris. These spiders often are found in and around human habitations. They like warm, undisturbed locations such as storage sheds or behind the clothes washer and dryer.

These spiders are not aggressive and bite only when threatened. Domestic pets usually are bitten when they lie down and trap the spider between the bedding and themselves. A single bite can inflict a lethal envenomation. Factors that appear to influence venom volume include the sex of the spider (males of equivalent size generate half the female volume) and its size (larger, mature spiders can deliver a larger volume).

When fractionated by gel electrophoresis, the venom consists of eight major protein bands and four minor bands. Sphingomyelinase D is the primary dermonecrotic factor. Sphingomyelinase D exerts its effect by binding to cell membranes and chemotactically influencing polymorphonuclear leukocytes. Another important mechanism is the inactivation of serum hemolytic complement. The venom induces rapid coagulation and occlusion of small capillaries, causing subsequent tissue necrosis. The toxin depletes serum hemolytic complement, prolongs the activated partial thromboplastin time, and depletes clotting factors VIII, IX, XI, and XII. When serum C-reactive protein and calcium are available, sphingomyelinase D has a direct hemolytic effect. The venom also acts on body lipids, freeing fragments into the circulation that subsequently act both as emboli and as inflammatory mediators. The victim's immune response to *Loxosceles* venom ultimately determines the severity of the ensuing lesion.

Early clinical diagnosis is difficult owing to the initially mild appearance of the lesion.[4] The ensuing severity of the 406 407 bite is controlled by three factors: the amount of venom injected, the bite site, and the victim's immune status.[3] Dogs are highly susceptible to the effects of the venom.

96.3.1 Clinical Signs

The victim may not be aware of being bitten by a brown recluse spider. There may be a mild stinging sensation for up to 8 hours after the bite. Subsequent pruritus and soreness develop as vasoconstriction causes local ischemia. Edema follows with a classic “bull's-eye” lesion (an erythematous area inside of which is a pale ischemic region that develops a dark necrotic center as the lesion matures). The erythematous margin may progress unevenly as the effects of gravity come into play. A hemorrhagic bulla may develop within 24 to 72 hours, with an eschar developing below. The eschar sloughs in approximately 2 to 5 weeks, leaving an indolent ulcer, which usually does not penetrate into the muscle.[3] Lesions in adipose tissue can be extensive. Healing is slow, and these ulcers may persist for months, leaving a deep scar. In humans local swelling and persistent segmental cutaneous anesthesia have resulted from envenomations to the neck and head region.

Systemic signs occur less commonly but can be life threatening. The most prevalent sign is a hemolytic anemia with significant hemoglobinuria, usually beginning within 24 hours after envenomation and persisting for approximately 1 week. The Coombs test result in animals with this anemia is usually negative. Other early-onset clinical signs include fever, arthralgia, vomiting, weakness, maculopapular rash, and leukocytosis. Disseminated intravascular coagulation and thrombocytopenia are possible sequelae. The systemic reaction is not proportionally related to the local reaction and vice versa.[3]

Pretreatment laboratory values should include a complete blood count, coagulation profile (e.g., prothrombin time, partial thromboplastin time, platelet count, fibrinogen), and a complete serum chemistry panel including electrolytes. The lesion should be measured. Tests with abnormal values or tests used to monitor the onset of hemolysis or hemoglobinuria (e.g., packed cell volume, red blood cell count, hemoglobin, visual serum evaluation, urinalysis) should be repeated as indicated to monitor the progression of the syndrome.

96.3.2 Treatment

There is no antidote. The treatment plan consists of responding to two possible syndromes, local cutaneous lesions and systemic manifestations of envenomation.

Dapsone (4,4′-diaminodiphenylsulfone), a leukocyte inhibitor, has been effective in treating dermal lesions in animal models.[4] In experimental studies, animals received 1 mg/kg dapsone by mouth for 14 days. The remaining ulcer was then allowed to heal as an open wound. Occasionally a second course of dapsone was indicated. It may be prudent to obtain a pretreatment hematocrit level and retest the patient in 2 or 3 days to monitor for a theoretical drug-induced hemolysis. By the time the maturing dermonecrotic lesion becomes manifest and the animal is brought for treatment, the clinical syndrome would be past the initial envenomation stage, which has the highest risk of venom-induced hemolysis.

Surgical excision has been advocated in the past but is no longer recommended. Results have been generally disappointing, and the procedure is not without complications. Conservative therapy includes several cleanings daily with Burow solution and hydrogen peroxide. One to two atmospheres of hyperbaric oxygen twice daily for 3 to 4 days may be beneficial.[4] Broad-spectrum antibiotics are indicated if dapsone is not being administered.

Systemic signs of *Loxosceles* envenomation are potentially fatal and should be addressed aggressively. Patients exhibiting such signs should be hospitalized for close observation. Antiinflammatory, antipyretic, and analgesic agents can be useful. Compounds that affect clotting should be avoided. Systemic glucocorticoids may have a protective effect on the red blood cell membrane, thereby inhibiting hemolysis. They should be used only during the first few days of the syndrome. Coagulation defects are managed as indicated. Hospitalization and intravenous fluids may be needed to maintain adequate perfusion to protect renal function.

Mycobacterial or bacterial infection, decubitus ulcer, third-degree burn, and pyoderma mimic the dermonecrotic wound of a spider bite. Systemic signs must be differentiated from other causes of hemolytic anemia (e.g., immune-mediated, zinc poisoning, onion poisoning) and fever of unknown origin.

96.4 SUGGESTED FURTHER READING*

1. DL Swanson, RS Vetter: Bites of brown recluse spiders and suspected necrotic arachnidism. *New Engl J Med*. **352**, 2005, 700, *A review of brown recluse spider bites—an excellent article for the interested reader*.

* See the CD-ROM for a complete list of references

106 Chapter 106 Sepsis

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106.1 KEY POINTS

- Sepsis is a clinical syndrome of systemic inflammation in response to infection (bacterial, viral, fungal, or protozoal). Much of the morbidity and mortality associated with sepsis is a result of the host's inflammatory response, in addition to damage from the infection itself.
- Lipopolysaccharide (LPS) from gram-negative bacteria is a potent initiator of the inflammatory cascade; however, gram-positive bacterial products are also capable of eliciting a strong inflammatory response. Host response to LPS results in initiation of a cytokine response that includes both proinflammatory and antiinflammatory cytokines. The clinical presentation depends on the balance between these opposing mediators.
- Untreated sepsis can progress to septic shock, which is characterized by hypotension, vascular leak, and microvascular sludging despite intravascular volume resuscitation. This circulatory impairment leads to tissue hypoperfusion, organ failure, and death.

106.2 INTRODUCTION

Sepsis, severe sepsis, and septic shock (see Chapter 107) are common causes of morbidity and mortality. The incidence of severe sepsis in humans in the United States is approximately 3 cases per 1000; the mortality rate is approximately 30% and is due to progression to septic shock and multiple organ failure.[1] The incidence of sepsis in veterinary medicine is unknown, but the mortality rates appear to be similar, ranging from 20% to 68%.[2-6] Recognition and early, aggressive intervention and supportive care are key to the treatment of sepsis and septic shock.

106.3 DEFINITIONS

Bacteremia: The presence of live bacterial organisms in the bloodstream

Sepsis: The clinical syndrome caused by infection and the host's systemic inflammatory response to it; may be of bacterial (Gram positive or Gram negative), viral, protozoal, or fungal origin

Severe sepsis: Sepsis complicated by dysfunction of one or more organs

Septic shock: Acute circulatory failure and persistent arterial hypotension (despite volume resuscitation) associated with sepsis

Systemic inflammatory response syndrome (SIRS): The clinical signs of systemic inflammation in response to infectious or noninfectious insults (e.g., trauma, pancreatitis, burns, snakebites, neoplasia, and heat stroke)

Multiple organ dysfunction syndrome (MODS): Physiologic derangements of the endothelial, cardiopulmonary, renal, nervous, endocrine, and gastrointestinal (GI) systems associated with the progression of uncontrolled systemic inflammation and disseminated intravascular coagulation (DIC)

106.4 DIAGNOSTIC CRITERIA FOR SEPSIS

Sepsis and the systemic inflammatory response syndrome(SIRS) are clinical syndromes, not diseases, and as such are inherently difficult to define. In 2001, the International Sepsis Definitions Conference produced consensus guidelines for definitions and terminology for syndromes associated with microbial infection and the host response to it.[7] Because of the difficulty in defining universal physiologic derangements associated with sepsis, the Consensus Committee produced a list of clinical and physiologic derangements to "attempt to codify the physical and laboratory findings that prompt an experienced clinician to conclude that an infected patient 'looks septic'"[7] (Box 106-1). These criteria were proposed for human patients. Therefore, although conceptually useful for veterinary patients, specific values have not been validated in these species.

106.5 STAGING SEPSIS

Following the 2001 International Sepsis Definitions Conference, the concept called *PIRO* was adopted to stage sepsis and to describe clinical manifestations of the infection and the host response to it.[7] In this model, PIRO is an acronym for *p*redisposition, *i*nsult or *i*nfection, *r*esponse, and *o*rgan dysfunction. This conceptual and clinical framework attempts to incorporate patient factors with the microbial insult in order to stage the disease process and to identify factors that may contribute to morbidity and mortality. The PIRO approach may employ advanced diagnostic techniques not yet available in veterinary medicine, but hopefully it can serve as a guideline until similar methods are available and validated (Table 106-1).

Predisposition refers to the patient-specific factors that increase the risk of developing or dying from sepsis. Factors to be considered include genetic factors, comorbid conditions, age, species, breed, gender, and even socioeconomic factors. For example, an immunosuppressed patient may be more likely to contract an infection and less likely to mount an appropriate immune response. Socioeconomic factors may also play a role; inadequate vaccination against canine parvovirus in the individual and in the community would increase the risk of a given dog contracting parvoviral enteritis in its local environment.

106.5.1 Box 106-1 Diagnostic Criteria for Sepsis[7]

Infection is documented or suspected and some of the following are present:

106.5.1.1 General Parameters

Fever

Hypothermia (especially in cats)

Tachycardia

Bradycardia (especially in cats)

Tachypnea

Altered mental status

Significant edema or positive fluid balance

Hyperglycemia in the absence of diabetes

Hypoglycemia

106.5.1.2 Inflammatory Parameters

Leukocytosis

Leukopenia

Normal white blood cell count with >10% immature neutrophils

Increased plasma C-reactive protein

Increased plasma procalcitonin

Hemodynamic parameters

Arterial hypotension

Elevated mixed venous oxygen saturation

Increased cardiac index

Organ dysfunction parameters

Arterial hypoxemia

Acute oliguria, creatinine increase

Hypercoagulability or hypocoagulability

Ileus (absent bowel sounds)

Thrombocytopenia

Hyperbilirubinemia

Tissue perfusion parameters

Hyperlactatemia

Decreased capillary refill time

Insult refers to site, type, and extent of infection. All of these factors may influence the extent and course of disease. For example, generalized peritonitis is more serious and extensive than an encapsulated infection at a feeding tube site. Compared with a community-acquired infection, a nosocomial infection may harbor bacteria that are more resistant to antimicrobial agents. A gram-positive or fungal infection will elicit a different host response than will a gram-negative infection.

Response refers to the host reaction to infection which may, in part, determine whether there is an adequate, inadequate, or overly exuberant inflammatory response. Additionally, there are regional and temporal differences in the immune response to infection, meaning that in some areas or times the response may be deficient (often termed *immune paralysis*) whereas in others the response may be overly exuberant, either of which may be harmful to the patient. The host response is characterized by biomarkers of inflammation (e.g., interleukin [IL]-6, C-reactive protein), measures of host responsiveness (e.g., CD11 and CD18, lymphocyte function), or detection of specific targets of therapy (e.g., protein C, antithrombin, cortisol response). Currently in veterinary medicine, relatively few biomarkers are available to assess host response.

Organ dysfunction refers to physiologic derangements secondary to the infection or to the host response or both. Organ dysfunction may be reversible. Classic examples of sepsis-associated organ dysfunction include DIC, acute respiratory distress syndrome, and acute renal failure.

Table 106-1 PIRO System for Staging Sepsis[7]

PIRO	Present	Future
Predisposition	Age, species, gender, breed, concurrent illness	Genetic susceptibility of the host to an abnormal or inappropriate inflammatory response and enhanced understanding of the host response to infection
Insult or infection	Culture and sensitivity of infecting organisms	Detection of microbial products (e.g., LPS, bacterial DNA)
Response	SIRS, clinical and clinicopathologic signs of sepsis and septic shock	Markers of inflammation (CRP, IL-6) Host responsiveness (ICAM-1, cortisol, LBP) Specific targets of therapy (APC)
Organ dysfunction	Clinicopathologic abnormalities suggesting organ dysfunction Number of failing organ systems	Measures of cellular response to insult or infection (cytopathic hypoxia, apoptosis)

APC, Activated protein C; *CRP,* C-reactive protein; *DNA,* deoxyribonucleic acid; *ICAM-1,* intercellular adhesion molecule-1; *IL-6,* interleukin-6; *LBP,* lipopolysaccharide-binding protein; *LPS,* lipopolysaccharide; *SIRS,* systemic inflammatory response syndrome.

106.6 EPIDEMIOLOGY

106.6.1 Septic Foci

In small animal medicine, the epidemiologic information in the literature describes the septic foci noted in Table 106-2.

106.6.2 Diseases Associated With Sepsis

Although there are numerous possible septic foci (see Chapters 108 to 116), septic peritonitis seems to be a common cause of sepsis in small animals, dogs more so than cats (see Table 106-2). Leakage of contents from the GI tract is reported to be the cause of septic peritonitis in 36% to 71% of dogs and cats and occurs secondary to GI neoplasia, ingestion of foreign bodies, dehiscence of biopsy sites, enterotomies or resected intestine, NSAID-associated ulcers, perforation of megacolon, and severe colitis.[4,10,11] Other reported causes of septic peritonitis include contamination from the urinary bladder, uterine rupture, GI disease such as salmonellosis or parvoviral enteritis and hepatic, pancreatic, splenic, and mesenteric lymph node abscess formation.[4,10-12] Aside from septic peritonitis, other, less common, causes of sepsis include pyelonephritis, pneumonia, septic arthritis, deep pyoderma, bacterial endocarditis, tick-borne diseases, vasculitis, septic meningitis, pyothorax, trauma, bite wounds, osteomyelitis, septic prostatitis, immune suppression, and gastrointestinal diseases such as salmonellosis or parvoviral enteritis.[2,4,8,9,13]

106.6.3 Bacteria Associated With Sepsis

Gram-negative enteric bacteria are the most commonly implicated organisms in sepsis in dogs and cats[2,10]; however, mixed infections and gram-positive infections are also described.[2,4,9-11] Culture of infected tissue should be obtained whenever possible (i.e., safe) because early and appropriate antibiotic selection is essential for preventing bacterial replication and the host inflammatory response to infection. Knowledge of common isolates may help guide empiric antibiotic selection (Table 106-3).

Table 106-2 Septic Foci

Site	Dogs (%)	Reference No.	Cats (%)	Reference No.
Abdomen	35 to 36	2, 8	17	9
Reproductive organs	10 to 25	2, 4	1 to 4	9, 10
Respiratory tract	20 to 28	2, 8	14	9
Pleural space, pyothorax	3 to 20	2, 8	24	9
Gastrointestinal system	52	4	17 to 47	9, 10
Endocarditis	—	—	14	9
Urinary tract	4 to 10	2, 8	7 to 8	9, 10
Pancreatic abscess	—	—	6	10
Trauma	29	4	3 to 50	4, 9, 10

Table 106-3 Characteristics of Bacterial Isolates in Septic Patients

Reference No.	No. Antemortem Samples Submitted for Bacterial Culture	Pure Gram Negative	Pure Gram Positive	Mixed	Most Common Isolates in Antemortem Bacterial Cultures
11	14	Not noted	Not noted	6/14	*Escherichia coli* (7) *Enterococcus* (4)
9	12	8/29[*]	11/29[*]	10/29[*]	*E. coli* (7) β-Hemolytic *Streptococcus* (3) *Pseudomonas* (2)
10	31	Not noted	Not noted	17/31	*E. coli* (17) *Enterococcus* (14) *Clostridium* (9)
2	20	7/20	5/20	7/20	*E. coli* (13) *Streptococcus* (8) *Enterococcus* (4)
4	19	3/19	1/19	15/19	*E. coli* (14) *Enterococcus* (13) *Clostridium* (4) α-Hemolytic *Streptococcus* (4)

[*] Bacteria were identified microscopically at necropsy in all 29 cases, whereas 12/29 were cultured antemortem.

106.7 PATHOGENESIS OF THE SEPTIC SYSTEMIC INFLAMMATORY RESPONSE

106.7.1 Microbial Factors

106.7.1.1 Gram-Negative Sepsis

Sources for gram-negative sepsis most commonly include the GI and genitourinary systems. The lipid A portion of lipopolysaccharide (LPS), a component of the gram-negative bacterial wall, is the most potent initiator of the septic inflammatory cascade known.[14] Host recognition and reaction to LPS involves LPS binding to lipopolysaccharide binding protein (LBP), followed by the LPS-LBP complex binding to membrane-bound CD14 on macrophages.[14-16] This binding activates the macrophage and initiates signaling transduction to the nucleus (via toll-like receptor [TLR]-4 and the transcription factor NF-κβ) to start transcription of inflammatory cytokines,[17] most notably tumor necrosis factor (TNF)-α, IL-1, IL-6, IL-8, and interferon-γ. In addition to proinflammatory mediators, the response also generates production of counter-inflammatory mediators (IL-4, IL-10, IL-13, transforming growth factor-β, and glucocorticoids).[16]

106.7.1.2 Gram-Positive Sepsis

Common sources for gram-positive sepsis include skin, injured soft tissue, and intravenous catheters. Activation of the inflammatory cascade by gram-positive bacteria occurs in response to cell wall components (lipoteichoic acid, peptidoglycan, peptidoglycan stem peptides) or via elaboration of soluble bacterial exotoxins.[18] TLRs (i.e., TLR-2) are also involved in the response to gram-positive bacteria.[19] Gram-positive bacterial exotoxins can act as "superantigens" and induce widespread activation of T-cells, leading to uncontrolled release of inflammatory cytokines such as interferon-γ and TNF-α.[16,18] Additionally, destruction of gram-positive organisms in the intracellular space requires cell-mediated immunity rather than the humoral response that is responsible for the killing of gram-negative organisms in the extracellular space.[18] 456

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106.7.2 Host Response to Bacterial Infection

Activation of macrophages initiates the septic systemic inflammatory response, and TNF-α production is a key factor in the early phase of sepsis.[20] LPS is the most potent stimulus for the release of TNF-α, which acts as an early central regulator of interactions among cytokines. Macrophage-derived cytokines, such as TNF-α, recruit other inflammatory cells (i.e., neutrophils, monocytes) to the affected area. Neutrophil responses to cytokine signaling can result in extensive host tissue damage secondary to the release of products such as reactive oxygen species, proteases, lysozymes, lactoferrin, cathepsins, and defensins. Neutrophils produce relatively small amounts of TNF-α, IL-1, and platelet-activating factor.

A controlled inflammatory response is beneficial to the host. Such a response is localized and represents a balance between activation of the inflammatory cascade and host mechanisms to counterregulate it. An excessive inflammatory response results from disproportionate activation of the proinflammatory mediators or lack of regulatory counterparts. On the other extreme, "immune paralysis" results from excessive antiinflammatory activity. Additionally, there may be regional and temporal differences in proinflammatory versus antiinflammatory activity.[21]

The clinical syndrome of sepsis results from systemic inflammation and is manifested by the cardinal signs of redness, heat, swelling, pain, and loss of function. Redness is from vasodilation; heat is due to vasodilation and increased metabolism (centrally and of local inflammatory cells); swelling is secondary to capillary permeability; pain is attributable to swelling, ischemia, and inflammatory mediators; and loss of function represents progression to multiple organ dysfunction syndrome. Ultimately, untreated or unresponsive sepsis can progress to septic shock, which is characterized by loss of vasomotor tone, vascular leak, hypotension, and hypoperfusion, all of which contribute to multiple organ failure and death (see Chapter 107, Septic Shock).

106.8 CLINICOPATHOLOGIC ABNORMALITIES

106.8.1 Complete Blood Cell Count, Coagulation Testing, and Hemostatic Changes

In humans with sepsis, the most common hematologic abnormalities are anemia, leukocytosis, thrombocytopenia, and activation of the hemostatic system.[21] The veterinary literature reports similar changes in dogs and cats.[2,9,10,23-25] Leukocytosis with an increased percentage of bands (left shift) and cytologic evidence of toxic neutrophils indicates active and premature release from the bone marrow and suggests progressive inflammation. Vasculitis, platelet sequestration in the lymphoreticular system, or DIC will contribute to thrombocytopenia. Blood loss (e.g., from a poorly perfused and ulcerated GI tract), hemolysis, and/or decreased red blood cell production contribute to anemia. Anemia is more common in septic cats; dogs may show hemoconcentration secondary to volume depletion, splenic contraction, or both. Causes of anemia in septic cats include premature clearance by the reticuloendothelial system causing a low-grade hemolysis and increased susceptibility to oxidative damage leading to a Heinz body anemia.[23-25]

Hemostatic dysfunction is an early manifestation of severe sepsis and is reported in virtually all human patients.[22,26] It also has been reported in dogs and cats with sepsis.[2,13] Sepsis-induced hemostatic changes are characterized by involves hypercoagulability initially, followed by hypocoagulability (see Chapter 107, Septic Shock). The initial hypercoagulable state is often overlooked, because it is generally subclinical and is difficult to diagnose or measure. The later hypocoagulable state is typified by the progression of a septic patient into DIC. Evidence of hemostatic abnormalities in septic dogs has been described.[2,13] One study showed that septic dogs had significantly lower protein C levels and antithrombin activities, and higher prothrombin time, partial thromboplastin time, D-dimer, and fibrin(ogen) degradation products than did controls.[2] Septic dogs did not differ from controls with respect to platelet counts.[2] Dogs with naturally occurring parvoviral enteritis had decreased antithrombin activity and increased maximum amplitude on the thromboelastogram, consistent with hypercoagulability.[13] Commonly available laboratory testing may elucidate these hematologic and hemostatic changes (Table 106-4).[22,26,27]

106.8.2 Serum Biochemistry

Changes in the biochemical profile often are reflective of the underlying disease process (e.g., azotemia with pyelonephritis) but may also be due to nonspecific sepsis-induced abnormalities (e.g., hyperbilirubinemia due to cholestasis). Ultimately, in severe sepsis and septic shock, the biochemical profile and other clinicopathologic tests will reveal organ dysfunction or failure (e.g., hepatic failure, DIC). Variable abnormalities in blood glucose concentration are reported in septic dogs. Typically, hyperglycemia precedes hypoglycemia. Decreased serum albumin concentrations have also been reported.[2,9] This hypoalbuminemia may be due to loss of albumin (either out of the body or into the interstitial space with increased vascular permeability), hepatic dysfunction, or preferential synthesis of acute phase proteins.[27] Hyperbilirubinemia is common in both human and small animal patients with sepsis.[2,9,29,30] Endotoxin is thought to induce a defect in hepatocellular transportation of conjugated bile to the canalicular membrane as evidenced by intrahepatic cholestasis with minimal (focal) or no hepatocyte necrosis.[29,30] Cats, on the contrary, do not display this characteristic histopathologic finding and do not develop biochemical changes (other than elevated bilirubin levels) consistent with cholestasis.[9] Consistent with the commonly seen anemia, hemolysis may explain the hyperbilirubinemia observed in septic cats.[9]

Table 106-4 Hematologic and Hemostatic Changes in Sepsis

Hematologic Parameter	Tests Available	Possible Abnormalities
WBC count	WBC count, differential Blood smear, cytologic evaluation Bone marrow evaluation	Leukocytosis or leukopenia Toxic changes, immature neutrophils Myeloid hyperplasia
Red blood cell count	Hematocrit Reticulocyte count Blood smear, cytologic evaluation Bone marrow evaluation	Hemoconcentration or anemia Nonregenerative anemia Heinz bodies (cats) Schistocytes Erythroid hypoplasia
Platelets	Platelet count Blood smear, cytologic evaluation	Thrombocytopenia
Hemostatic parameters	PT	Normal (early) or prolongation (late)
	PTT	Normal (early) or prolongation (late
	Activated coagulation time	Normal (early) or prolongation (late)
	FDP	Increased
	D-Dimers	Increased (late)
	Antithrombin*	Decreased activity
	Thromboelastography*	Increased coagulation index
	Protein C*	Decreased

FDP, Fibrinogen degradation products; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *WBC,* white blood cell.

* Less commonly performed tests; may be available only through reference laboratories.

106.8.3 Biomarkers in Sepsis

There is a need for earlier detection of sepsis because early clinical signs such as tachypnea, tachycardia, fever, and leukocytosis are nonspecific, and later markers of severe sepsis such as organ dysfunction, arterial hypotension, or hyperlactatemia are associated with high mortality. Broad categories of markers might include markers of infection (e.g., LPS, bacterial deoxyribonucleic acid), markers of cellular responsiveness (intercellular adhesion molecule, LBP, CD11, and CD18),[8] and products of inflammatory cells and humoral activation (interleukins, antithrombin, activated protein C).[2] Ideal biomarkers of sepsis detect the presence of infection, severity of infection, and progression from sepsis to severe sepsis and septic shock. Optimally, biomarkers monitor response to treatment and provide a prognostic index. The marker should also correspond temporally with the unique dynamic course of disease in individuals. Procalcitonin fulfills many of these parameters for human sepsis, but their role in veterinary patients is yet to be defined.[31] IL-6 rises early and persists with ongoing inflammation and is specific for the severity of the inflammatory response, but not for bacterial infection.[32] Serum IL-6 is increased in experimental models of endotoxemia or inflammation in dogs; IL-6 begins to rise within hours and stays elevated for days in the face of persistent inflammation.[32-34] Activated protein C is decreased in many septic human patients and represents a target of therapy that reduces mortality in some populations with severe sepsis.[35] Treatment, however, is expensive and species specific. C-reactive protein, an acute phase protein, has been used in dogs as a marker of inflammation, but is not specific for infection.[36] In cats, C-reactive protein does not appear to be involved in the acute phase response.[37] Other possible biomarkers in sepsis include bacterial endotoxin (LPS), LBP, nitrate and nitrite concentrations (by-products of nitric oxide metabolism), intercellular adhesion molecules, antithrombin, tissue factor pathway inhibitor, CD14, CD11b/CD18, T-cell function assays, and IL-12.

106.9 BACTERIAL CULTURE, SENSITIVITY, AND ANTIMICROBIAL AGENTS

Of paramount importance is the identification of the septic focus and, whenever possible, procurement of infected tissue for bacterial culture and sensitivity. Note that, in some patients, collection of tissue may be impossible because of patient cardiovascular instability or hypocoagulability. Although culture of infected tissue is ideal, cytologic or histopathologic nexamination may also be used to make a definitive diagnosis of infection.[4,9-11] In selecting empiric antibiotics for a septic patient while awaiting culture and sensitivity results, the following factors should be considered: (1) the location of the septic focus and the expected bacterial flora in that tissue, (2) the ability of the antibiotic to penetrate that tissue, (3) recent history of antibiotic use and considerations for resistance, and (4) source of infection (whether nosocomial or community acquired). One study highlighted the importance of appropriate antibiotic selection; in five cases in which inappropriate antibiotics were administered empirically, the mortality rate was 80%.[4] Delaying administration of antibiotics or withholding their use in a septic patient increases the ability of those bacteria to reproduce, spread, and induce a greater inflammatory response.

106.10 CONCLUSION

The incidence of severe sepsis is approximately 3 cases per 1000 people, and the mortality rate is approximately 30%; death is due to progression to septic shock and multiple organ failure.[1] The incidence of sepsis in veterinary medicine is unknown, but the reported mortality rates range from 20% to 68%.[2-4] Earlier detection of sepsis is essential to control infection and inflammation, thus preventing the progression from sepsis to severe sepsis and septic shock. Studies of sepsis need to focus on species differences in host response and progression. Identification of biomarkers to assist in diagnosis, monitoring, and prognosis is critical to improved treatment of this potentially fatal syndrome.

106.11 SUGGESTED FURTHER READING*

CA Brady, CM Otto, TJ Van Winkle, et al.: Severe sepsis in cats: 29 cases (1986-1998). *J Am Vet Med Assoc*. **217**, 2000, 531, *An important retrospective study that identified major differences in clinical findings among dogs and cats with sepsis.*

JJ Ceron, PD Eckersall, SM Subiela: Acute phase proteins in dogs and cats: current knowledge and future perspectives. *Vet Clin Pathol*. **34**, 2005, 85, *A review of the acute phase response and clinical applications of monitoring acute phase proteins in dogs and cats.*

MF Costello, KJ Drobatz, LR Aronson, et al.: Underlying cause, pathophysiologic abnormalities and response to treatment in cats with septic peritonitis: 51 cases (1990). *J Am Vet Med Assoc*. **225**, 2004, 897, *A retrospective clinical study that found certain features of septic peritonitis in cats to be unique, such as a relative bradycardia, absence of abdominal pain on palpation, and apparent spontaneous septic effusion.*

AM de Laforcade, LM Freeman, SP Shaw, et al.: Hemostatic changes in dogs with naturally occurring sepsis. *J Vet Intern Med*. **17**, 2003, 674, *A prospective case control study that found hemostatic changes in dogs with naturally occurring sepsis as compared with controls*.

* See the CD-ROM for a complete list of references

107 Chapter 107 Septic Shock

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107.1 KEY POINTS

- Septic shock is defined as sepsis-associated acute circulatory failure and persistent arterial hypotension despite intravascular volume resuscitation.
- The clinical pictures of severe sepsis and septic shock differ between dogs and cats.
- Endothelial dysfunction and coagulation abnormalities are an important part of the clinical and pathophysiologic derangements that occur in patients with septic shock.
- The mechanisms by which the clotting system interacts with the immune system have greatly facilitated the understanding of coagulation and the pathophysiology of septic shock, however much remains to be discerned.

107.2 INTRODUCTION

Septic shock is the clinical syndrome of sepsis-associated acute circulatory failure. Vasoactive drugs typically are required to manage the arterial hypotension that persists despite appropriate volume resuscitation. In severe sepsis, dysfunction of at least one organ system is present. The mortality rate of humans in the advanced stages of sepsis (i.e., severe sepsis and septic shock) exceeds 30%.[1] Although estimates of mortality in dogs and cats range from 20% to 68%, sepsis in small animal patients has not been stratified according to severity (i.e., sepsis versus severe sepsis versus septic shock).[2-6] Widespread endothelial disruption and activation of the coagulation cascade and complement systems are involved in the progression of the inflammatory process and, ultimately, in the progression from sepsis to septic shock. In addition to the loss of vasomotor tone, the clinical syndrome of septic shock is characterized by increased capillary permeability, microvascular sludging, and hypotension. This circulatory impairment leads to hypoperfusion, tissue ischemia, organ failure, and death.

107.3 DEFINITIONS

Bacteremia: Live bacterial organisms present in the bloodstream

Systemic inflammatory response syndrome (SIRS): The clinical signs of systemic inflammation in response to infectious or noninfectious insults (e.g., trauma, pancreatitis, burns, snake bites, neoplasia, and heat stroke) exhibited

Sepsis: The clinical syndrome caused by infection of the host by microorganisms and the host's inflammatory response to it; microorganisms may be bacterial, viral, protozoal, or fungal

Severe sepsis: Sepsis complicated by dysfunction of one or more organs

Septic shock: Acute circulatory failure and persistent arterial hypotension (despite volume resuscitation) associated with sepsis

Multiple organ dysfunction syndrome (MODS): The physiologic derangements of the endothelial, cardiopulmonary, renal, hepatic, nervous, endocrine, and gastrointestinal(GI) systems associated with the progression of uncontrolled systemic inflammation and disseminated intravascular coagulation (DIC)

107.4 PATHOPHYSIOLOGY, CLINICAL SIGNS, AND STAGES OF SEPTIC SHOCK

107.4.1 Early Septic Shock

Septic shock, by definition, implies arterial hypotension and circulatory failure despite adequate intravascular volume resuscitation. It is the final and most extreme stage in the continuum between sepsis and septic shock. Earlier in the course of sepsis, clinical signs result from SIRS, and these patients may appear hemodynamically stable.[3,4,7] Neurohumoral responses that contribute to physiologic compensation during early septic shock include a baroreceptor-mediated release of catecholamines which, in turn, leads to production of counterregulatory hormones such as glucagon, adrenocorticotropic hormone, and cortisol.

Unlike cats in the early stages of sepsis, dogs manifest a hyperdynamic and hypermetabolic response that is typified by tachycardia, tachypnea, hyperemia, decreased capillary refill time, and pyrexia.[3,4,7,8] Cats, on the other hand, are more likely to be lethargic, bradycardic, hypothermic, and pale, with weak pulses.[8]

107.4.2 Early Decompensated Sepsis

During this phase of septic shock, compensatory responses fail and the patient develops hypotension and hypoperfusion. Indirect indicators of tissue hypoperfusion are hyperlactatemia and decreased central (or mixed) venous oxygen saturation.[9,10] Central venous oxygen saturation of less than 70% suggests that oxygen delivery is in a supply-dependent state and may result in anaerobic metabolism and consequently lactate production.[9]

Sepsis results in maldistribution of blood flow. Preferential distribution of blood flow to the heart and brain may lead to poor perfusion to the kidneys, GI, liver, and skin. Heterogenous flow within organs also occurs. In addition, endothelial dysfunction, activation of white blood cells, and coagulation can lead to microthromboses and capillary obstruction, interfering with perfusion of tissues and organs. Oxygen delivery is further compromised by interstitial tissue edema secondary to increased capillary permeability.

Clinically, the mucous membranes become pale, pulse quality is poor, and the patient is mentally depressed. Clinicopathologic changes suggestive of organ dysfunction or failure may start to appear (azotemia, oligoanuria, hyperbilirubinemia, disseminated intravascular coagulopathy [DIC]).

107.4.3 Late Decompensated Septic Shock

As the patient makes the transition into late decompensated septic shock, refractory hypotension and multiple organ failure may develop and lead to death. The brain and heart lose their preferential blood flow, and a complete loss of vasomotor control and severe impairment of cardiac contractility occur. Renal hypoperfusion causes oligoanuria; acute respiratory distress syndrome (ARDS) and pulmonary edema cause respiratory failure. Clinically, the patient becomes hypothermic, stuporous or comatose, has pale mucous membranes with slow or no capillary refill time, and pulses are waning.

107.5 SEPSIS AND COAGULATION

Disorders of coagulation and fibrinolysis play an important role in the development of organ dysfunction in sepsis and septic shock. Pathogenic pathways leading to coagulation disorders in severe sepsis and septic shock include: (1) activation of the coagulation cascade, (2) defective physiologic anticoagulant pathways, and (3) impaired fibrinolysis. Clinically, activation of these pathways can lead to an early hypercoagulable or prothrombotic state that is difficult to diagnose but can contribute to organ dysfunction through inflammatory mediators and microthrombi. As sepsis progresses, the coagulation disorders reflect a consumptive coagulopathy, impairment of anticoagulant mechanisms, and inhibition of fibrinolysis that is recognized clinically as DIC[11-16] (see Chapter 117, Hypercoagulable States).

107.6 ORGAN DYSFUNCTION IN SEPTIC SHOCK

107.6.1 Cardiovascular Dysfunction

The cardiovascular system can be affected by the circulating cytokines associated with sepsis in three important ways: (1) the vasculature becomes more permeable, allowing for fluid transudation across the endothelium into extravascular spaces, leading to hypovolemia and tissue edema, (2) the contractility of the heart becomes impaired leading to poor cardiac output, and (3) the vasculature becomes incapable of maintaining tone, causing maldistribution of blood flow. At one time the impaired cardiac performance seen in septic animals and humans was thought to be due to a single “myocardial depressant factor,” but the effects on cardiac performance are thought to be due to the actions of not one, but many, circulating cytokines (e.g., tumor necrosis factor-α, interleukin (IL)-1β, IL-2, and IL-6).[17]

107.6.2 Respiratory Dysfunction

Acute lung injury (ALI) and the more severe condition, ARDS, are manifestations of lung injury that occur during sepsis and SIRS (see Chapter 24, Acute Lung Injury and Acute Respiratory Distress Syndrome). ALI and ARDS are labels that describe the syndrome of SIRS-associated or sepsis-associated lung injury, rather than disease processes themselves. The distinction between the two is merely the severity of compromise in gas exchange. The pathogenesis of impaired gas exchange in ALI and ARDS involves endothelial and epithelial injury, neutrophil-dependant lung injury, proinflammatory cytokines, abnormalities of the coagulation system, and abnormalities in the production, composition, and function of surfactant.[18] Ultimately there is an accumulation of protein-rich fluid in the alveoli and infiltration of the alveolar interstitial space with inflammatory cells, fluid, and debris that may be seen radiographically as alveolar infiltrates. The lungs are the "shock organ" in cats and are especially vulnerable to injury during sepsis; tachypnea was a common finding in one study looking at cats with severe sepsis and, although only 11 of 29 cats had an underlying respiratory cause (pneumonia or pyothorax), 17 of 29 had clinical or radiographic signs of respiratory disease.[8] Septic cats commonly are fluid intolerant and quite susceptible to fluid overload.

107.6.3 Renal Dysfunction

Acute renal failure (ARF) is a common sequela to sepsis and SIRS in humans. There are no veterinary clinical studies reporting the incidence of ARF in sepsis, however clinical impression and retrospective studies suggest that sepsis-induced ARF is not very common in dogs and cats.[8,19,20] Historically, the proposed underlying pathogenic mechanism of sepsis-associated ARF has been related to acute tubular necrosis secondary to renal ischemia (e.g., either due to afferent arteriolar vasoconstriction, microthrombi, and/or poor cardiac output).[21] Sepsis-associated ARF may be more complicated than a simple reduction in renal blood flow.[21] Tissue injury may be due to ischemia-reperfusion injury or activation of macrophages and neutrophils or both, alterations in nitric oxide metabolism, cytopathic hypoxia, and renal apoptosis.[22] ROS may contribute to vasoconstriction directly or through depletion of endogenous vasodilators such as prostacyclin and nitric oxide. Apoptotic pathways may be activated in response to potentially lethal insults (e.g., tumor necrosis factor, ischemia, toxins).[22]

107.6.4 Neurologic Dysfunction

Neurologic dysfunction associated with sepsis is poorly characterized and poorly understood. Central nervous system abnormalities (decreased alertness, stupor, coma, seizures) are common in people with septic shock. Anatomic, histopathologic, and reversible changes such as a reduction in cerebral blood flow, capillary leakage, and dysfunction of the blood-brain barrier may be responsible for the neurologic dysfunction of septic patients.[23,24] It is unknown whether these same mechanisms apply to dogs and cats.

107.6.5 Gastrointestinal and Hepatic Dysfunction

GI dysfunction can manifest as ileus, poor tolerance to enteral feedings, vomiting, diarrhea, GI ulceration, melena, and hematochezia. Malnutrition, fluid and electrolyte losses, and small intestinal bacterial overgrowth 460 can result from these gastrointestinal disturbances. GI permeability may be increased, thereby predisposing to 461 bacterial translocation into the lymphatic system and the bloodstream. Mechanisms of increased GI epithelial permeability and hepatic dysfunction may include dysregulation of blood flow, alterations in energy metabolism, oxidant stress, or direct effects of cytokines promoting apoptosis.[25,26] The liver is thought to be the "shock organ" in dogs. Hepatic dysfunction can result in hypoalbuminemia, coagulopathies, hypoglycemia, icterus, mental depression, and encephalopathies. Decreased albumin levels may also result from loss into the extravascular space, a shift toward acute phase protein production and secondary to lipopolysaccharide downregulation of transcription factor NF-κβ.

107.6.6 Microcirculatory Dysfunction

Normally vascular endothelial cells play key roles in antithrombosis, profibrinolysis, and inhibition of platelet and leukocyte aggregation. In patients with sepsis, systemic inflammation impairs the ability of the vascular endothelium to perform these critical functions, often resulting in DIC (see Chapter 117, Hypercoagulable

States). In addition, sepsis-induced alterations in vascular endothelial function and perfused capillary density may result in capillary leak syndromes and heterogenous blood flow within organs. Pathologic oxygen supply limitation may occur as a result of decreases in both diffusive (i.e., tissue edema) and convective (i.e., decreased perfused capillary density) oxygen delivery.[27] In this sense, endothelial dysfunction can be implicated as the “motor” of MODS. New technology such as sidestream darkfield imaging enables visualization and assessment of microcirculatory derangements during sepsis and in response to therapy.

Table 107-1 Circulatory Support in Septic Shock

Fluid Therapy	Indications	Dose	Comments
Isotonic crystalloids	Intravascular volume replacement Interstitial fluid deficits MainAtenance	*Dog:* Up to 60 to 90 ml/kg* *Cat:* Up to 40 to 60 ml/kg*	May precipitate interstitial edema in patients with capillary leak or a low COP
Synthetic colloids (e.g., hydroxyethyl starch, dextran-70)	Volume replacement Colloid osmotic support	*Dog:* 5 to 20 ml/kg* *Cat:* 5 to 10 ml/kg*	Dose-related coagulopathies have been documented An arbitrary recommendation is ≤20 ml/kg q24h
Human albumin solution (HSA)	Colloid osmotic support Volume replacement Albumin supplementation	2 ml/kg/hr of 25% HSA for 1 to 2 hours followed by 0.1 to 0.2 ml/kg/hr × 10 hours Or, calculate albumin deficit: Alb deficit (in grams) = 10 × (desired Alb – patient Alb) × wt (kg) × 0.3 and replace over 4 to 6 hours	Doses extrapolated from human literature Monitor closely for reactions
Fresh frozen plasma	Coagulopathies Factor deficiencies Supplemental volume and colloid osmotic support	10 to 15 ml/kg as needed	Not effective at increasing albumin concentration
Packed red blood cells	Anemia	10 to 15 ml/kg will raise PCV by ~10%	—
Fresh whole blood	Anemia Thrombocytopenia Coagulopathies and factor deficiencies Volume replacement	20 ml/kg will raise PCV by ~10%	—

Modified from Brady C, Otto CM: Systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction, *Vet Clin North Am Small Anim Pract* 31:1147, 2001.

Alb, Albumin; *HSA,* human albumin serum; *PCV,* packed cell volume.

* Listed intravenous fluid doses are “shock doses.” Generally, a fraction of the listed dose is given (e.g., one fourth to one half) and response is assessed; the dose is repeated as necessary or until fluid tolerance is reached. Cats seem to have a poor pulmonary tolerance to volume resuscitation, therefore smaller doses may be tried first.

107.7 TREATMENT OF SEPTIC SHOCK

107.7.1 Circulatory Support

Because septic patients are, by definition, in circulatory collapse despite volume resuscitation, cardiovascular support is a primary objective. Aggressive fluid therapy is essential to maintain adequate tissue oxygen delivery and to prevent the development of MODS and death. Isotonic crystalloids, hypertonic crystalloid solutions, synthetic colloids, and blood component therapy may be used during fluid resuscitation and maintenance in the septic patient (Table 107-1). The choice of fluids depends on the overall clinical and clinicopathologic picture (see Chapters 64 and 65, Daily Intravenous Fluid Therapy and Shock Fluids and Fluid Challenge, respectively).

The patient with septic shock often has increased vascular endothelial permeability and hypoalbuminemia, and this must be considered. Hypoalbuminemia may necessitate the use of synthetic colloids (e.g., hydroxyethyl starch or dextran-70 solutions) or blood component therapy (e.g., human albumin or fresh frozen plasma). Large volumes of fresh frozen plasma are required for albumin replacement (i.e., 22 ml/kg of plasma to raise the albumin concentration by 0.5 g/dl).[28] Fresh frozen plasma is therefore used only to prevent a further decline in albumin in severely hypoalbuminemic patients and for correction of coagulopathies and factor deficiencies.

Human serum albumin is in the early stages of clinical use in veterinary medicine and research is ongoing. The 25% human serum albumin solution is hyperoncotic (100 mm Hg) and should be used judiciously in patients with limited fluid tolerance. Coagulopathies, anemia, and thrombocytopenia may prompt the use of blood component therapy (e.g., fresh frozen plasma, packed red blood cells, fresh whole blood). A central venous catheter will allow monitoring of trends in central venous pressures during aggressive fluid therapy. A Swan-Ganz catheter or noninvasive cardiac output monitoring may be even more helpful because trends in systemic vascular resistance, cardiac output, and pulmonary capillary wedge pressure can be obtained, thereby guiding decisions regarding the use of fluids, pressors, and inotropic agents (see Chapter 203, Hemodynamic Monitoring).

Accurate monitoring of body weight and urine output via an indwelling urinary catheter is also helpful in assessing total fluid balance as well as monitoring for oligoanuric renal failure. It should be noted, however, that urinary output is a result of the balance between preglomerular and postglomerular resistance. Thus a marked increase in postglomerular resistance can induce an increase in urinary output in the presence of renal hypoperfusion.

Hypotension that persists after intravascular volume has been restored is an indication for vasopressors or inotropic agents to support flow to tissues (see Chapters 6, 176, and 177, Hypotension, Vasoactive Catecholamines, and Vasopressin, respectively). The decision to use a vasopressor or an inotrope depends on the clinical presentation and on objective information obtained from the septic patient. Vasopressors such as norepinephrine, dopamine, phenylephrine, and vasopressin are used in patients with peripheral vasodilation (see Table 107-1). Clinical evidence of peripheral vasodilation includes bright red mucous membranes, bounding pulses, and fast capillary refill times, although cats do not exhibit these signs.

Invasive or noninvasive measurements of systemic vascular resistance will help guide decisions regarding vasopressors. Vasopressors may maintain arterial blood pressure but may also result in excessive vasoconstriction, particularly to the splanchnic circulation, thereby causing GI ischemia and GI dysfunction as described above. Particularly in the dog, splanchnic vasoconstriction may exacerbate the septic state by promoting loss of gut barrier function and bacterial translocation.

Positive inotropic agents such as dobutamine generally are used in patients with evidence of impaired myocardial contractility (decreased fractional shortening on M-mode echocardiography, decreased cardiac output per invasive or noninvasive measurements).

107.7.2 Antimicrobial Use in Sepsis

Of paramount importance in treating the septic patient is the identification of the septic focus and, whenever possible, procurement of infected tissue or fluid for bacterial identification and determination of antibiotic sensitivity. In some patients, sample collection may be impossible because of cardiopulmonary instability or coagulopathy. While awaiting culture and sensitivity results, empiric antibiotic therapy should be selected based on the following factors: antibiotic properties (cidal versus static), the expected bacterial flora in the affected tissue, the ability of the antibiotic to penetrate the infected tissue, recent history of antibiotic use and considerations for resistance, and source of infection (whether nosocomial or community acquired) (see Chapter 194, Antimicrobial Use in the Critical Care Patient). When inappropriate empiric therapy was chosen in five canine cases, four of the dogs died,[4] highlighting the importance of appropriate antibiotic selection. Septic patients require a broad-spectrum bactericidal antimicrobial regimen that is administered via the intravenous route (see Chapters 195 to 200). Below are some examples of four-quadrant therapy (i.e., therapies that are effective against gram-positive and gram-negative aerobes and anaerobes). All dosages are listed for the *intravenous* route:

- Ampicillin (22 mg/kg q8h) and enrofloxacin (5 to 20 mg/kg q24h; 5 mg/kg q8h in cats)
- Ampicillin (22 mg/kg q8h) and amikacin (15 mg/kg q24h)
- Ampicillin (22 mg/kg q8h) and gentamicin (6.6 mg/kg q24h)
- Cefazolin (22 mg/kg q8h) and amikacin (15 mg/kg q24h)
- Cefazolin (22 mg/kg q8h) and gentamicin (6.6 mg/kg q24h)
- Ampicillin (22 mg/kg q8h) and cefoxitin (15 to 30 mg/kg q4-6h)
- Ampicillin (22 mg/kg q8h) and cefotaxime (25 to 50 mg/kg q4-6h)
- Ampicillin (22 mg/kg q8h) and ceftazidime (30 to 50 mg/kg q6-8h)
- Clindamycin (8 to 10 mg/kg q12h) and enrofloxacin (5 to 20 mg/kg q24h; 5 mg/kg q24h in cats)
- Clindamycin (8 to 10 mg/kg q12h) and amikacin (15 mg/kg q24h)
- Clindamycin (8 to 10 mg/kg q12h) and gentamicin (6.6 mg/kg q24h)
- Ticarcillin and clavulanic acid (50 mg/kg q6h) and enrofloxacin (5 to 20 mg/kg q24h; 5 mg/kg q24h in cats)
- Imipenem (5 to 10 mg/kg q6-8h)
- Meropenem (8 to 12 mg/kg q8-12h)

107.8 TREATMENT STRATEGIES

A number of landmark studies in human medicine during the last 6 years seem to have improved outcome in critically ill patients with sepsis and septic shock (Table 107-2).

107.9 CONCLUSION

The progression from sepsis to severe sepsis and septic shock involves an early phase in which the patient appears hemodynamically stable because of neurohormonal compensatory mechanisms that maintain cardiovascular tone. The later stages involve widespread endothelial disruption, progressive inflammation, and activation of the coagulation cascade. Throughout the progression from sepsis to septic shock, there is extensive interplay between the coagulation and immune systems. In addition to the loss of vasomotor tone, the clinical syndrome of septic shock is characterized by increased capillary permeability, microvascular sludging, and hypovolemia. This circulatory impairment leads to hypoperfusion, tissue ischemia, organ failure, and death. Attempts to treat septic shock are aimed at supporting the cardiovascular system while treating the underlying infection. There are several new and promising approaches to treatment of sepsis and septic shock.

Table 107-2 Important Studies of Sepsis and Septic Shock in Human Medicine

Study	Major Finding
Early goal-directed therapy in sepsis[9]	Showed decreased mortality and severity of illness with goal-directed therapy ($S_{CV}O_2$, CVP, Hct, MAP, S_aO_2, and urine output) early in the treatment of septic patients
Relative adrenal insufficiency in sepsis[29]	Showed improved 28-day mortality rate and shortened duration of vasopressor administration in patients with septic shock who failed to respond to ACTH stimulation when pharmacologic doses of corticosteroids were used
Tight glycemic control in sepsis[33-37]	Demonstrated decreased morbidity and mortality rates and incidence of sepsis with intensive insulin therapy to strictly regulate glucose levels in critically ill surgical patients
Physiologic anticoagulants in sepsis[14,38-40]	Showed that administration of recombinant activated protein C reduces mortality in patients with septic shock, although it is associated with an increased risk of serious bleeding[14,40]

ACTH, Adrenocorticotropic hormone; *CVP,* central venous pressure; *Hct,* hematocrit; *MAP,* mean arterial pressure; S_aO_2, arterial oxygen saturation; $S_{CV}O_2$, central venous oxygen saturation.

107.10 SUGGESTED FURTHER READING*

CA Brady, CM Otto: Systemic inflammatory response syndrome, sepsis and multiple organ dysfunction. *Vet Clin North Am*. **6**, 2001, 1147, *An overview of the pathophysiology, clinical findings, diagnosis, and treatment of SIRS, sepsis, and MODS.*

CA Brady, CM Otto, TJ Van Winkle, et al.: Severe sepsis in cats: 29 cases (1986-1998). *J Am Vet Med Assoc*. **217**, 2000, 531, *An important retrospective study that identified major differences in clinical findings between dogs and cats with sepsis.*

K Hopper, S Bateman: An updated view of hemostasis: mechanisms of hemostatic dysfunction associated with sepsis. *J Vet Emerg Crit Care*. **15**, 2005, 83, *A comprehensive overview of sepsis-associated derangements in hemostasis*.

EM Mazzaferro, E Rudloff, R Kirby: The role of albumin replacement in the critically ill veterinary patient. *J Vet Emerg Crit Care*. **12**, 2002, 113, *A comprehensive review of the physiologic role of albumin and effects of therapeutic albumin supplementation*.

E Rivers, B Nguyen, S Havstag, et al.: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. **345**, 2001, 1368, *An important and highly publicized prospective study that compared early hemodynamic resuscitation directed by indirect markers of global perfusion and oxygen delivery*.

* See the CD-ROM for a complete list of references

108 Chapter 108 Gram-Positive Infections

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108.1 KEY POINTS

- Most gram-positive infections are caused by normal resident microflora of the skin, mucous membranes, and gastrointestinal tract.
- Critically ill hospitalized patients are at increased risk for infections with opportunistic gram-positive bacteria.
- *Streptococcus canis* is a well-recognized cause of various suppurative infections in animals, including toxic shock syndrome.
- Enterococci, traditionally viewed as commensal bacteria in the alimentary tract of animals, are now known to be capable of causing life-threatening, multidrug-resistant infections in dogs and cats.
- As antibiotic-resistant staphylococci and enterococci evolve, the ability to treat gram-positive infections in companion animals using cephalosporins and penicillins is decreasing.
- Considering the increasing antibiotic resistance in gram-positive bacteria, it is imperative to implement antibiotic therapy wisely, using the appropriate dosage, dosing interval, and duration of therapy.

108.2 INTRODUCTION

Since the early 1990s the epidemiology of pathogenic bacteria isolated from critically ill patients has shifted from gram-negative organisms to an increasing number of nosocomial infections caused by gram-positive isolates.[1-3] Increasing numbers of pathogenic, multidrug-resistant (MDR) gram-positive organisms are now being isolated from both dogs and cats, paralleling the trend in antibiotic-resistant nosocomial and community-acquired infections in humans.[1,4-6] Recognition of emerging trends of resistance, particularly in *Enterococcus faecium* and various strains of staphylococci, not only militates against indiscriminate antimicrobial use, but should permit the clinician to select a sound empiric antibiotic regimen for critically ill patients suffering from such infections.[2,3,5,7-9]

108.3 GRAM-POSITIVE CELL STRUCTURE AND PATHOGENICITY

Morphologically, gram-positive bacteria are composed of a cell wall, a single cytoplasmic membrane, and cytosol. The cell wall is a thick, coarse structure that serves as an exoskeleton.[1] Buried within the cell wall are enzymes called *transpeptidases,* commonly referred to as *penicillin-binding proteins (PBPs)*. [1,10] PBPs are a group of enzymes responsible for the building and maintenance of the cell wall.

In addition to a thick cell well, most gram-positive bacteria have other protective mechanisms.[10,11] One of these mechanisms is an outer capsule or biofilm that extends beyond the cell wall itself and interfaces with the external milieu.[1,11] Hydrolase enzymes located within the cytoplasmic membrane, called *β-lactamases,* serve a protective role for the bacteria.[1,11] Once attacked by the hydrolases, the β-lactam antibiotics are no longer capable of binding to PBPs in normally susceptible bacteria.[1,10,12]

Peptidoglycan is the basic structural component of the cell wall of gram-positive bacteria, accounting for 50% to 80% of the total cell wall content.[10,11] Like endotoxin, peptidoglycan is released by bacteria during infection, reaches the systemic circulation, and exhibits proinflammatory activity.[11] Lipoteichoic acids found in the gram-positive cell wall have both structural and epithelial adherence functions.[10] Lipoteichoic acid induces a proinflammatory cytokine response, the production of nitric oxide, and may lead to cardiovascular compromise.[10]

In addition to structural components, gram-positive organisms produce soluble exotoxins that may play a role in the pathogenesis of sepsis. Much attention is focused on the roles of superantigenic exotoxins that promote the massive release of cytokines, potentially leading to shock and multiorgan failure in both human and veterinary patients.[10,12,13]

108.4 STREPTOCOCCAL INFECTIONS

The genus *Streptococcus* consists of gram-positive cocci arranged in chains. These are fastidious bacteria that require the addition of blood or serum to culture media.[10,14,15] They are nonmotile and non–spore forming. Most are facultative anaerobes and may require enriched media to grow. Streptococci are generally commensal organisms found on the skin and mucous membranes, and are ecologically important as part of the normal microflora in pets and humans.[14,15] However, several species of streptococci are capable of causing localized or widespread pyogenic infections in companion animals.[15]

Streptococci may be grouped superficially by how they grow on blood agar plates as either hemolytic or nonhemolytic.[10,12] The type of hemolytic reaction displayed on blood agar has been used to classify the bacteria as either α-hemolytic or β-hemolytic. β-Hemolytic species are generally pathogenic, and nonhemolytic or α-hemolytic members of the genera have been viewed traditionally as contaminants or unimportant invaders when isolated.[12,15]

Streptococci are also classified serologically based on species-specific carbohydrate cell wall antigens, with groups designated A through L.[14,15] Group A streptococci *(Streptococcus pyogenes)* cause pharyngitis, glomerulonephritis, and rheumatic fever in humans.[12,14] Although dogs may become colonized transiently with this organism, group A streptococci rarely cause illness in dogs and cats.[10,12,14,15] Therapy is not generally indicated, but these organisms are susceptible to most β-lactam agents, macrolides, and chloramphenicol; resistant strains may be treated with cephalosporins.[15]

Similarly, group B or C streptococci are rare causes of illness in immunocompetent pets.[14,15] Infections with group B *Streptococcus agalactiae* have been associated with neonatal sepsis and fading puppy syndrome.[15] Sporadically, cases of endometritis, wound infections, pyelonephritis, lymphadenitis, neonatal sepsis, and pneumonia due to infection with β-hemolytic group C streptococci have been documented in dogs and cats.[16,17] Species included in this serologic group include *Streptococcus equi* subsp *zooepidemicus,* and *Streptococcus dysgalactiae*. [14,16,17] Although culture and susceptibility testing is always advocated, effective therapies for these infections are generally the same as those described for the group A streptococci.[15,17]

Group G streptococci are common resident microflora and are the cause of most streptococcal infection in dogs and cats.[10,12,15] The most common isolate is *Streptococcus canis*. [10,15] The main source of infection with this pathogen in dogs is the anal mucosa, with young cats more commonly acquiring infection from the vagina of the queen or via the umbilicus.[15] Infection spreads rapidly in neonatal kittens and is often fatal during the first week of life in affected cats.[15] *S. canis* may be isolated from adult cats with abscesses, urinary tract infections, arthritis, metritis, or mastitis, and from kittens with lymphadenitis, pneumonia, or neonatal septicemia.[10,15]

S. canis is generally an opportunistic pathogen of dogs and is isolated from an array of nonspecific infections, including wounds, the mammary gland, urogenital tract, skin, and ear canal.[15] *S. canis* is also responsible for canine prostatitis, mastitis, abscesses, infective endocarditis, pericarditis, pyometra, sepsis, discospondylitis, and meningoencephalomyelitis.[11,15,18] *S. canis* has been implicated in cases of fading puppy syndrome, causing polyarthritis and septicemia in affected pups.[15]

Despite 50 years of penicillin use in animals, there is no documented mechanism of resistance to the drug in β-hemolytic group G streptococci; penicillin G and ampicillin are therefore effective for most infections.[2,11,15] Chloramphenicol, potentiated sulfonamides, and most cephalosporins are also usually efficacious. Susceptibility to veterinary-approved fluoroquinolones is negligible and generally discouraged.[19] *Streptococcus* spp are generally not considered susceptible to aminoglycosides, owing to poor transport across the cytoplasmic membrane.[2] However, the synergistic combination of a β-lactam agent with an aminoglycoside remains an appropriate treatment for animals with streptococcal bacteremia or endocarditis.[2] In critically ill patients with disseminated infection, long-term (≥6 weeks) therapy is generally indicated. Combination therapy is recommended for cases of infective necrotizing fasciitis (see section on Empiric Antibiotic Strategies later in chapter), endocarditis, or when polymicrobial infections are suspected.

Streptococcal toxic shock syndrome (STTS), with or without necrotizing fasciitis, is recognized as an emerging syndrome in dogs (see Chapter 115, Necrotizing Soft Tissue Infections).[10,15] The most common infection in animals with STTS appears to be the lung, with affected dogs suffering from acute or peracute suppurative bronchopneumonia. Some case histories have included failed attempts to treat patients with enrofloxacin and nonsteroidal antiinflammatory agents.[15,19] Cases of STTS-associated septicemia are often fatal, whereas most dogs with necrotizing fasciitis alone survive with rapid, appropriate medical therapy and aggressive surgical resection.[20]

The most likely pathogenesis for STTS and necrotizing fasciitis starts with minor trauma. The dog then licks its wounds and seeds *S. canis* from the oral mucosa into the wound.[20,21] The bacteria proliferate, typically resulting in painful, rapidly developing cellulitis, skin discoloration, and often signs of systemic illness.[15,20,21] Prompt recognition and aggressive surgical debridement are imperative.[15] Clindamycin has proven to be a valuable treatment in affected animals.[15] Chloramphenicol, erythromycin, and β-lactam antibiotics also may be effective.[15] Culture and susceptibility testing is important, because similar toxic shock–like diseases in dogs may be caused by bacteria other than streptococci. Gram staining of tissues or fluids should be helpful in ascertaining the morphology of the infecting agent, particularly in acute infections.[15] A similar syndrome in young cats with suppurative lymphadenopathy caused by group G streptococci has been reported.[10,15]

108.5 ENTEROCOCCAL INFECTIONS

Enterococcus species are facultative anaerobic cocci that demonstrate intrinsic and acquired resistance to multiple antibiotics.[8] Enterococci (previously group D streptococci), as the name implies, are commensal bacteria that inhabit the alimentary tract of animals and humans.[4,10,14] Enterococcal infections were previously considered rare, and not especially virulent, in companion animals.[14] They typically are recovered from mixed infections in which it is difficult to assess their role; they are assumed to be commensal organisms “along for the ride” with other more virulent organisms such as anaerobes and gram-negative enteric bacteria. Such a priori assumptions can no longer be made, because pathogenic and drug-resistant enterococci are recovered increasingly from hospitalized patients.[3,4] Similarly, the presence and expression of virulence genes in some enterococcal species implies that these organisms are an important consideration in the treatment of serious gram-positive infections.[3,4,7,14,15]

Postoperative wound and urogenital infections are seen most commonly; however, enterococcal cholangiohepatitis, peritonitis, vegetative endocarditis, mastitis, and blood-borne infections have been reported in companion animals.[4,15] Many enterococci are intrinsically resistant to numerous antibiotics, and the development of MDR enterococci is thought to result from both inappropriate antibiotic usage and poor infection control measures in hospitalized patients.[2-4,8,10] The vast majority of clinical isolates belong to the species *Enterococcus faecalis,* although *E. faecium* remains the species that exhibits a disproportionately greater resistance to multiple antibiotics.[7,8]

E. faecium is largely of interest because of increasing resistance to vancomycin, which until recently was effective for almost all penicillin-resistant enterococci.[10] Strains that remain sensitive to vancomycin may be resistant to a wide range of drugs that are commonly selected for empiric treatment of intensive care patients.[7,8] Although the veterinary literature is sparse, there are recent and serious concerns of acquired antibiotic resistance by *E. faecalis* and *E. faecium*. There is a lack of host specificity among various bacterial strains that suggests that cross-colonization of resistant strains may occur from one species to another.[7,8,22] *E. faecium* often possesses inherent and acquired resistance to many drug classes, including the fluoroquinolones, clindamycin, macrolides, and potentiated sulfonamides.[7,8] Unlike most streptococci, the enterococci are often inhibited, but not killed, by penicillins and are generally resistant to cephalosporins.[2] Moreover, although enterococci do not intrinsically produce β-lactamases, production of these enzymes by the bacteria may be induced by exposure to β-lactamase inhibitor drugs. As such, it is of no benefit to prescribe amoxicillin-clavulanate or ampicillin-sulbactam if the pathogen is sensitive to the aminopenicillin alone.

Of the 52 *E. faecium* isolates obtained from clinical patients at the Ryan Veterinary Hospital of the University of Pennsylvania, 71% were resistant to ampicillin (S. Rankin, personal communication). One of the few effective modes of therapy takes advantage of antibiotic synergy; penicillins alone only arrest their growth and aminoglycosides are without effect except at very high concentrations, but the combination of both drugs effectively kills the organism.[4] This high-dosage synergy approach is among the most effective pharmacologic means to clear infection and, unless there is compelling evidence that other potentially safer antibiotic regimens are effective both in vivo and in vitro, the combination of gentamicin plus a cell wall–active agent (generally ampicillin) remains a gold standard for critically ill veterinary patients.[22]

Unfortunately, some enterococci are becoming resistant to aminoglycosides, even when coadministered with ampicillin, leaving the clinician with few alternatives to eradicate the infection.[4] In some cases, the only effective drugs are glycopeptides, such as vancomycin, but this drug should be viewed as an absolute last resort.[4,8] Vancomycin has a narrow spectrum and is potentially nephrotoxic (see Chapter 200, Miscellaneous Antibiotics).[1] Clinical experience with vancomycin is limited in veterinary medicine.

108.6 STAPHYLOCOCCAL INFECTIONS

The broad distribution of staphylococci as normal flora of domestic animals is perhaps the most important epidemiologic factor in staphylococcal infections.[3,6,11,12] These organisms are generally not inherently invasive and colonize intact epithelium of healthy animals without causing disease.[6,10,12] Subsequently, isolation of these bacteria may signify the presence of transient contaminants or long-term colonization of epithelial surfaces.[6,11]

Disease pathogenesis and lesion development are incompletely understood, but likely involve a breach of the host's mucosal barrier or other means of immunocompromise, in conjunction with numerous bacterial virulence factors such as staphylococcal toxins and enzymes that permit them to withstand phagocytosis by neutrophils.[10-12] For many years, production of coagulase by staphylococci has been associated with virulence and tissue tropism, and almost all infections in humans, dogs, and cats were caused by coagulase-positive species, with coagulase-negative staphylococci viewed invariably as contaminants.[11,12,23] More recent studies have implicated coagulase-negative staphylococci as a cause of significant infection in humans and companion animals.[2,3,9,18,23]

Pathogenic staphylococci may affect any organ system and are responsible for community-acquired and nosocomial infections. Pyogenic staphylococcal infections occur most commonly in the skin, eyes, ears, and respiratory and genitourinary tracts.[12] Osteomyelitis, meningoencephalitis, bacteremia, and endocarditis have also been reported.[12,18] Of approximately 35 species of staphylococcal organisms, 3 are of clinical importance in companion animals: *Staphylococcus aureus, Staphylococcus intermedius,* and *Staphylococcus schleiferi* subspecies *coagulans*. [9,10,24] *S. intermedius* is the leading pyogenic bacterium of dogs.[10] Although it is recognized as the most common etiologic agent of bacterial skin and ear infections, it is may also cause systemic infections including arthritis, osteomyelitis, cystitis, mastitis, and bacteremia.[5,10] Sites of infection are similar in cats, although reports of disseminated disease are less numerous.

Infections with strains of *S. intermedius* that are resistant to virtually all β-lactam agents are becoming more common.[5] Approximately 40% of *S. intermedius* strains isolated from dogs are simultaneously resistant to three or more antibiotics. Antibiotic resistance patterns have emerged for pyoderma and systemic infections caused by *S. schleiferi* as well.[9] Although this bacterium appears to be a less frequent cause of disseminated infections, results of clinical studies reveal that tissue tropism and antimicrobial susceptibility data are not predictable for this relatively novel species.[9] *S. aureus,* however, is well established as a significant community-acquired and nosocomial pathogen in humans, and infection with methicillin-resistant *S. aureus* (MRSA) is an ominous development in veterinary medicine.[5,6,9,24,25]

Not all *S. aureus* organisms are methicillin resistant. Moreover, other staphylococcal species may be classified as methicillin resistant. Determination of methicillin resistance is based on in vitro resistance to oxacillin.[25] If staphylococci are resistant to oxacillin, they are considered resistant to all other β-lactams, including cephalosporins and amoxicillin-clavulanate, regardless of the results of in vitro susceptibility testing.[6] Although dogs and cats are not natural reservoirs of *S. aureus,* they can become colonized, in all likelihood from humans.[6,24] Once colonized, pets may clear the organism, go on to develop infection, or remain asymptomatic carriers for an indeterminate period.[5,24]

Virulent MDR staphylococcal infections are isolated most commonly from hospitalized patients, or patients that have a history of antibiotic use. Surgical wound, bronchopulmonary, and genitourinary tract infections caused by MRSA are documented more commonly, although any body system is susceptible to infection by these opportunistic bacteria.[6] Staphylococcal resistance to β-lactam agents is due to the possession of a plasmid-encoded β-lactamase, or the presence of a chromosomal element that contains the gene that encodes for a penicillin-resistant PBPs.[6,9,12,24]

Infected animals should be isolated, and barrier contact precautions should be used when handling patients, food bowls, bandages, and all associated materials. Handwashing between patients is imperative. Such guidelines must be enforced (1) to minimize the risk of patient-to-patient spread of resistant clones and (2) to limit the likelihood of animal-to-human transmission. There is increasing evidence that interspecies transmission of MRSA occurs and that it may be emerging as an important zoonotic and veterinary disease.[5,6,25]

In human hospitals, transmission occurs mainly via the transiently colonized hands of health care workers. Colonized veterinary personnel are thought to be the most likely vectors of MRSA in veterinary hospitals.[6,24,25] All personnel in contact with patients should be advised of appropriate precautions once MRSA infection is confirmed.[9,25] Like other staphylococci, MRSA can survive for long periods on inanimate objects such as bedding and cages, 466
and it is relatively resistant to heat. Thus it is difficult to eliminate once introduced to the hospital environment. 467
MRSA infections, although serious, most often remain treatable, albeit by a small number of antibiotics.[5,6,25] Because MRSA may be transmitted between animals and humans, owners of infected or colonized animals should be informed of this potential.[6] However, veterinarians are discouraged from making any recommendations regarding the diagnosis or treatment of MRSA, or any disease, in humans.

Treatment of deep or disseminated staphylococcal infection requires systemic therapy.[10,12] Drug choices should be based on in vitro susceptibility testing in combination with other factors (e.g., drug penetration, site of infection). Historically, uncomplicated methicillin-susceptible staphylococcal infections are predictably responsive to β-lactam and β-lactamase inhibitor combination drugs and first-generation cephalosporins.[12] These are drugs of first choice for routine infections when staphylococcal infection is suspected. Clindamycin, azithromycin, potentiated sulfonamides, tetracycline, gentamicin, and the fluoroquinolones are frequently, although not uniformly, effective for treating most staphylococcal infections.[1,10,26] This level of confidence cannot extend to hospitalized patients with risk factors for MDR, such as those with a history of antibiotic use, indwelling devices, exposure to nosocomial pathogens, and protracted hospital stays.[12]

Culture and susceptibility testing is imperative for such patients, regardless of the drug being considered for therapy.[12] The proliferation of methicillin resistance in *S. aureus, S. schleiferi,* and *S. intermedius* suggests that empiric therapy guidelines require revision, because resistance to many non–β-lactam antibiotics occurs in these genera as well.[2,9] Significantly, methicillin-resistant *S. intermedius* and MRSA are increasingly resistant to fluoroquinolones and macrolides.[1,2,9,12] Commercial veterinary laboratories should test all β-lactam–resistant staphylococci for susceptibility to chloramphenicol, clindamycin, tetracycline, and potentiated sulfonamides. Preliminary reports should be available within 2 days for standard aerobic cultures submitted under appropriate conditions.[10,12] Duration of therapy depends on the site of infection and comorbid conditions that may impair host defenses or delay healing. When tolerated, therapy extends 2 weeks beyond the resolution of clinical signs of infection.

Although vancomycin and linezolid remain the only effective antibiotics for MDR strains in human health care settings, these drugs should be used only in exceptional circumstances in veterinary medicine. It is argued that their use should restricted in dogs and cats, because avoidance of antibiotic use is a valid strategy to curtail antibiotic resistance.[12] Consultation with a microbiologist or clinical pharmacologist is strongly recommended before determining that therapy with either of these drugs is indicated for a given patient.

108.7

EMPIRIC ANTIBIOTIC STRATEGIES

In the critically ill patient, broad-spectrum empiric antimicrobial therapy is warranted when the pathogen is not known or when polymicrobial infection is suspected(Table 108-1). Wright-Giemsa and gram-stained cytologic preparations of aspirates or impression smears should be examined to evaluate the morphologic and staining characteristics of bacterial pathogens.

Table 108-1 Antibiotics Used to Treat Gram-Positive Infections

Drug	**Dosage**
Amikacin	15 to 20 mg/kg IV q24h
Ampicillin	22 mg/kg IV q6-8h
Ampicillin-sulbactam	22 mg/kg IV q8h
Azithromycin	5 to 10 mg/kg IV q24h
Cefazolin	22 mg/kg IV q6-8h
Cefotetan	30 mg/kg IV q8h
Cefoxitin	30 mg/kg IV q6-8h
Chloramphenicol	25 to 50 mg/kg IV q8h (dogs) 15 to 20 mg/kg IV q12h (cats)
Clindamycin	10 mg/kg IV q8-12h
Enrofloxacin	12.5 to 20 mg/kg IV q24h (dogs) 5 mg/kg IV q24h (cats)
Gentamicin	6.6 mg/kg IV q24h
Imipenem-cilastatin	5 to 10 mg/kg IV q6-8h
Meropenem	8 to 12 mg/kg IV q8-12h
Ticarcillin-clavulanate	50 mg/kg IV q6-8h
Vancomycin	15 mg/kg IV q8h (dogs) 10 to 15 mg/kg IV q8h (cats)

IV, Intravenous.

Clinicians should be familiar with the gram-positive pathogens associated with severe infections in their hospital and choose therapy based on the prevalence and susceptibility patterns of these bacteria, and the site(s) of infection. Once culture and susceptibility data are available, therapy is streamlined to ensure eradication of the pathogen without promoting resistance secondary to inappropriate antibiotic treatment.

Although bacterial resistance to previously effective antibiotics is an ever-increasing concern in patients with gram-positive infections, first-choice recommendations in critically ill veterinary patients still include a first-generation cephalosporin (e.g., cefazolin), aminopenicillin, or a β-lactam and β-lactamase inhibitor combination (e.g., ampicillin-sulbactam). The first-generation cephalosporins have a similar spectrum of activity to ampicillin, with the notable difference that β-lactamase–producing staphylococci often remain susceptible to the cephalosporins.[12] However, methicillin-resistant coagulase-positive staphylococci are resistant to all cephalosporins.[1]

Sulbactam, like clavulanic acid, is an inhibitor of β-lactamases.[1] These drugs have weak antibacterial activity by themselves, but show extraordinary synergism when administered with ampicillin, amoxicillin, or ticarcillin, because they irreversibly bind the β-lactamase enzymes of many resistant bacteria.[1,11] The aminopenicillins and first-generation cephalosporins have relatively short half-lives, and in the absence of renal impairment they should be administered every 6 hours to take advantage of the well-described pharmacodynamic properties of most β-lactam agents. This recommendation is particularly relevant for patients with altered volumes of distribution (i.e., patients on intravenous fluids, parenteral nutrition or blood products, and those with vascular leak or third-spacing syndromes).

Alterations in drug clearance can occur rapidly, and the clinician must consider these and other pharmacokinetic principles when determining dosages of all antibiotics so that the desired pharmacodynamic effects can be reached.[1]

A notable exception to the above therapeutic recommendations occurs when there is documentation of a new infection in a patient that is already receiving one of these drugs. Similarly, critically ill patients with a history of antibiotic therapy or polymicrobial infection may be treated appropriately with broader-spectrum antibiotics, such as a carbapenem, alone or in conjunction with an aminoglycoside or fluoroquinolone, while culture and susceptibility results are pending.

Both fluoroquinolones and aminoglycosides remain effective treatment for some staphylococci.[26] Neither drug class is predictably active against streptococci. They do, however provide very good coverage for gram-negative pathogens that may be contributing to patient morbidity. These agents generally are administered once daily at the upper end of the dosage range. Enrofloxacin should not be administered at high dosages to cats, because its administration has been associated with temporary or permanent blindness in domestic felids.

Among the aminoglycosides, gentamicin is generally more effective than amikacin for staphylococcal infections. Both are associated with potential renal dysfunction, but they frequently are prescribed without incident for short-term therapy (≤7 days) in well-hydrated patients without preexisting renal disease. Gentamicin, when administered with ampicillin, is effective for many serious enterococcal infections, as discussed earlier. Clindamycin is active against aerobic and anaerobic gram-positive organisms and is an appropriate first-line agent for patients with bone infections or β-lactam intolerance.

Carbapenems, such as imipenem and meropenem, possess good activity against most *Streptococcus* and *Staphylococcus* spp. However, they are uniformly ineffective for MRSA or vancomycin-resistant enterococcal organisms. They are prescribed based on culture and susceptibility data, or prescribed empirically in patients with risk factors for infection with MDR pathogens.[1,2] They should not be used liberally, however, because excessive use of carbapenems is associated with β-lactamase production against other β-lactam antibiotics, especially cephalosporins.[1]

Chloramphenicol and potentiated sulfonamides are generally not used empirically in the critically ill patient, but some MDR staphylococci are susceptible to these agents. Both have been prescribed for many years, and practitioners are encouraged to familiarize (or refamiliarize) themselves not only with their spectrum of activity, but also with the uncommon but potentially serious adverse events that may occur with their use. All enterococci are inherently resistant to potentiated sulfonamides. Vancomycin is seldom required to treat isolates of any of the gram-positive cocci in veterinary medicine.

Pharmaceutical companies are devoting fewer resources to the development of new antibiotics, and very few novel drugs are in the pipeline. With this in mind, there are no known indications for veterinarians to prescribe any of the antibiotics for virulent MDR enterococci or staphylococci recently approved for human medicine. Daptomycin, quinupristin-dalfopristin, linezolid, and tigecycline are the last lines of defense for patients with life-threatening infections (see Chapter 200, Miscellaneous Antibiotics). A small number of human *E. faecium* and *S. aureus* isolates possess documented resistance to these drugs, and clinicians are thus urged to use antibiotics rationally and wisely.[1,2]

108.8

SUGGESTED FURTHER READING*

HU Cox: Staphylococcal infections. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. ed 3, 2006, Saunders, St Louis, *A concise yet comprehensive chapter in an authoritative textbook that includes mechanisms of staphylococcal pathogenicity, diagnostic criteria, clinical syndromes, therapy, and public health considerations*.

CE Greene, JF Prescott: Streptococcal and other gram-positive bacterial infections. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. ed 3, 2006, Saunders, St Louis, *A chapter that includes the identification of and contemporary classification criteria for clinically significant streptococci. Clinical syndromes due to both* Streptococcus *spp. and* Enterococcus *spp. discussed in detail*.

DO Morris, KA Rook, FS Shofer, et al.: Screening of *Staphylococcus aureus, Staphylococcus intermedius,* and *Staphylococcus schleiferi* isolates obtained from small companion animals for antimicrobial resistance: a retrospective review of 749 isolates 2003). *Vet Dermatol*. **17**, 2006, 332, *A retrospective study from a veterinary referral hospital that highlights disturbing trends in antibiotic resistance—notably, that many methicillin-resistant staphylococci are commonly resistant to other major classes of antimicrobial agents*.

JS Weese: Methicillin-resistant *Staphylococcus aureus:* an emerging pathogen in small animals. *J Am Anim Hosp Assoc*. **41**, 2005, 150, *Written by an expert on this topic, a comprehensive review article that contrasts human and small animal MRSA infections. Concerning patterns of antibiotic resistance, clinical diagnosis, patient management, and concerns for nosocomial transmission addressed thoroughly*.

N Woodford: Biological counterstrike: antibiotic resistance mechanisms of gram-positive cocci. *Clin Microbiol Infect*. **11**(Suppl 3), 2005, 2, *An incisive review of relevant literature that consolidates the epidemiology and myriad antibiotic resistance mechanisms encountered in the treatment of streptococcal, enterococcal, and staphylococcal infections in humans. Veterinary personnel, especially those who routinely prescribe or dispense antibiotics in referral settings, encouraged to read this article*.

* See the CD-ROM for a complete list of references.

109 Chapter 109 Gram-Negative Infections

Reid P. Groman, DVM, DACVIM

109.1 KEY POINTS

- Endotoxin is a potent stimulator of the inflammatory response and is believed to initiate the pathology of gram-negative sepsis.
- Immunosuppression, hospitalization, invasive procedures, and prior antibiotic administration are thought to be risk factors for colonization and infection with multidrug-resistant gram-negative bacteria.
- Empiric therapy for gram-negative pathogens is aimed at optimizing outcome and limiting the development of resistance.
- Appropriate parenteral antibiotic therapy for first-time gram-negative infections includes cefazolin or ampicillin-sulbactam, alone or in combination with an aminoglycoside or fluoroquinolone.
- Antibiotic therapy for resistant nosocomial pathogens includes the carbapenems, third-generation cephalosporins, β-lactam–β-lactamase inhibitor combinations, and aminoglycosides.
- Increasing rates of antibiotic resistance among gram-negative pathogens threaten the efficacy of empiric antibiotic therapy in both the inpatient and outpatient settings.

109.2 INTRODUCTION

Infections due to gram-negative organisms are a significant cause of morbidity and mortality in critically ill patients.[1] Important aerobic or facultatively anaerobic gram-negative infections are often due to an opportunistic invasion by commensal intestinal flora, including *Escherichia coli, Proteus* spp, *Pseudomonas aeruginosa, Serratia* spp, and *Klebsiella* spp.[1,2] Less commonly, opportunistic infections are caused by environmental saprophytes that enter the body through wounds or the respiratory tract.[3]

109.3 GRAM-NEGATIVE CELL STRUCTURE AND PATHOGENICITY

In addition to having a cytoplasmic membrane and peptidoglycan layer similar to that found in gram-positive organisms, gram-negative bacteria possess unique factors that contribute to their ability to cause disease.[2-5] Among the bacterial products commonly implicated in the pathogenesis of gram-negative organisms is endotoxin, a unique lipopolysaccharide (LPS) that accounts for 75% of the outer surface of the gram-negative cell membrane.[4] The role of LPS in triggering the cellular and physiologic host responses is well established.[2,3,5,6]

Structurally, endotoxin consists of an outer polysaccharide chain that is bound to lipid A. Although it is buried deep in the bacterial cell wall, lipid A is known to be the toxic moiety of endotoxin.[3,4] Lipid A induces a wide range of proinflammatory responses (i.e., release of cytokines and activation of the compliment cascade) and endothelial dysfunction.[3,4,6] During minor or local infections with small numbers of bacteria, small amounts of LPS are released, leading to controlled cytokine production. The cytokines released promote body defenses by stimulating inflammation, fever, and appropriate protective immunologic responses.[3] However, during severe systemic infections with large numbers of bacteria, increased amounts of LPS are released, resulting in excessive, and sometimes maladaptive, cytokine production by monocytes and macrophages.[2-5] Harmful effects of endotoxin include vasodilation, enhanced vascular permeability, tissue destruction, and activation of coagulation pathways.[2,3,6]

Failure to contain or eradicate the microbe often results in further damage due to the inexorable progression of inflammation and infection.[2,4,5] Thus, of the many therapeutic interventions, early initiation of appropriate antibiotic therapy is of utmost importance to ensure a favorable outcome.[7,8]

Gram-negative organisms also possess cellular structures that are often recognized as virulence factors.[2,3,5,9] Flagella are protein filaments that extend from the cell membrane. Flagella allow for locomotion, undulating in a coordinated manner to move the bacteria toward or away from a chemical gradient, a process called *chemotaxis*. Pili (also called *fimbriae*) are straight filaments arising from the bacterial cell wall. Pili most often serve as adherence factors, in which case they are referred to *adhesins*. [2,5] For many bacteria, adhesins are vital to their ability to cause disease. Capsules are protective walls, generally composed of simple sugar residues that surround the cell membranes.[2,3] Encapsulation enhances virulence by preventing bacterial phagocytosis by host neutrophils and macrophages.[5]

109.4 IDENTIFICATION OF GRAM-NEGATIVE BACTERIA OF MEDICAL IMPORTANCE

The classification of gram-negative bacteria is based on several criteria, including their appearance on selective media, utilization of carbohydrates (e.g., lactose), production of certain end products (e.g., acids and alcohols), and the presence or absence of specialized enzymes (e.g., oxidase).[3,5] Although the clinical relevance of these categories is a point for contention among clinicians, taxonomic schemes permit the microbiology laboratory to distinguish rapidly among commonly encountered bacteria.[3,5,10] For example, facultatively anaerobic oxidase-negative, gram-negative rods that grow on MacConkey agar are presumed to be members of the Enterobacteriaceae.[3,5,9] As more information accumulates, reclassification of bacteria among genera and species and the creation of new designations must be accepted as part of scientific progress.[2]

109.5 ENTEROBACTERIACEAE

Members of the family Enterobacteriaceae are the most frequently encountered gram-negative isolates recovered from clinical specimens.[1,3,7] These commensal organisms are found in soil and water, on plants and, as the family name implies, within the intestinal tract of animals and humans.[2,3]

Before the advent of antibiotics, chemotherapy, and immunosuppressive measures, the infectious diseases caused by the Enterobacteriaceae were relatively well defined and typically characterized by diarrhea and other gastrointestinal syndromes.[2,5] However, members of the Enterobacteriaceae are now incriminated in virtually any type of infectious disease and may be recovered from any tissue or fluid specimen submitted to the laboratory.[3,5,9,11] By definition, commensal organisms colonize an individual without causing disease.[12] However, in a vulnerable host these “pathogenic commensals” have the capacity to produce disease.[1,7] Generally, enhanced bacterial virulence factors or damage to the mucosal barrier or immune system of the host is required for infection to occur.[2,5,9] Critically ill and immunocompromised patients are susceptible to hospital-acquired infections, following colonization with environmental strains or invasive procedures such as catheterization, endoscopy, and surgery.[2,5,7,12]

Escherichia coli is the most commonly encountered bacteria ium clinical microbiology laboratories and is thought to be the most important of the facultative aerobic gram-negative species that comprise the normal flora of the alimentary tract in most dogs and cats.[5,9,13] Most strains of *E. coli* are of low virulence, but they may cause opportunistic infections in extraintestinal sites.[5,7,11,13]

E. coli organisms were previously susceptible to select drugs. However, multidrug-resistant *E. coli* have emerged as a cause of opportunistic infections in companion animals.[14,15] Presently, the proportion of *E. coli* resistant to aminopenicillins, fluoroquinolones, and cephalosporins is increasing and causing great concern in both human and veterinary medicine.[16] Indiscriminate use of antibiotics, inadequate hygiene, and extended hospital stays are among the proposed reasons for resistance to these commonly used agents (see Chapter 194, Antimicrobial Use in the Critical Care Patient).[7,12,14-18] Empirically, amoxicillin-clavulanic acid, ampicillin-sulbactam, or fluoroquinolones may be prescribed appropriately for first-time infections, pending susceptibility data. In critically ill hospitalized patients with a history of antibiotic therapy, the presence of multidrug-resistant (MDR) organisms should be presumed.[7,11] In such circumstances, the prescribing of a third-generation cephalosporin or aminoglycoside is considered appropriate while culture and susceptibility information is pending.

Infections with serovars of *Salmonella enterica* are uncommon in dogs and cats. Serovars of *S. enterica* can survive for relatively long periods in the environment, and transmission through food, water, or fomites contaminated by fecal material likely plays a role in disease pathogenesis. Importantly, the prevalence of *Salmonella* in canine fecal samples varies widely and does not correlate with clinical disease. Young dogs are more susceptible to infection and clinical signs.

Factors that increase susceptibility to salmonellosis include poor nutrition, anesthesia, overcrowding, concurrent disease, and prior or contemporaneous drug therapy. The severity of signs varies from none to subacute diarrhea and septic shock. Fever, lethargy, and anorexia may be followed by abdominal pain, vomiting, hemorrhagic diarrhea, and dehydration. Central nervous system (CNS) signs, polyarthritis, and pneumonia may be seen. Aggressive supportive care is the cornerstone of therapy, and appropriate antibiotic therapy might include chloramphenicol, amoxicillin, or the potentiated sulfonamides.

Among the 16 species included in the genus *Enterobacter, E. aerogenes* and *E. cloacae* are the species most commonly encountered in clinical infections. MDR *E. cloacae* has been recovered from the urinary tract, respiratory tract, and surgical wounds of veterinary patients.[12,18] *E. cloacae* strains are inherently resistant to amoxicillin, amoxicillin-clavulanate, narrow-spectrum cephalosporins, and cefoxitin. Additionally, *E. cloacae* may acquire resistance to broad-spectrum β-lactams, especially when they are subjected to antibiotic pressure.[19] Pending final susceptibility data, the antimicrobial agents most indicated in the treatment of serious *Enterobacter* infections are carbapenems and fourth-generation cephalosporins. Aminoglycosides, fluoroquinolones, and the potentiated sulfonamides are frequently, although less predictably, effective. Third-generation cephalosporins frequently show good in vitro activity against these organisms but, as explained earlier, a significant risk of developing resistance during therapy exists.

Klebsiella spp are ubiquitous in nature and may be regarded as normal flora in the alimentary canal, biliary tract, and pharynx in dogs and cats.[2] *K. pneumoniae* is a primary pathogen; this property is thought to be related to its large antiphagocytic capsule. Patients with *K. pneumoniae* infection frequently have predisposing conditions, including immunosuppression, indwelling devices, chronic respiratory disease, or extended hospital stays.[7]

Although *K. pneumoniae* can cause severe pneumonia, it is more commonly the cause of hospital-acquired wound or urinary tract infections.[2,12] Extensive use of broad-spectrum antibiotics in hospitalized patients has led to both increased carriage of *Klebsiella* and, subsequently, the development of MDR strains that produce extended-spectrum β-lactamases (ESBLs).[7,20] The bowel is the most common site of colonization, with secondary infection of the urinary tract, respiratory tract, peritoneal cavity, biliary tract, wounds, and bloodstream.[12]

Proteus includes five species. The most common clinical isolates are *P. vulgaris* and *P. mirabilis*. Both are recovered from infected sites in immunocompromised hosts, particularly those receiving prolonged regimens of antibiotics. The recovery of an indole-negative *Proteus* spp can be presumptively identified as *P. mirabilis*. This is of clinical importance because most strains of *P. mirabilis* are sensitive to ampicillin and the cephalosporins, whereas *P. vulgaris* is predictably resistant to these drugs.

Serratia marcescens is recognized as an important opportunistic pathogen with invasive properties and a tendency to be resistant to many commonly used antibiotics. *Serratia* spp have been linked to nosocomial infections in both dogs and cats.[2]

109.6 NONFERMENTING GRAM-NEGATIVE BACTERIA

The nonfermenting gram-negative bacteria are a group of aerobic, non–spore-forming bacilli that either do not use carbohydrates as a source of energy or degrade them through metabolic pathways other than fermentation.[10,21] 470 Unlike the Enterobacteriaceae, the nonfermenting gram-negative bacilli 471 do not fit conveniently into a single family of well-characterized genera, and the correct taxonomic placement of many of these organisms remains unresolved.[9,10]

Most often, gram-negative nonfermenters are niche pathogens that cause opportunistic infections in critically ill or immunocompromised patients.[7,10,12,21] Unlike the Enterobacteriaceae, gram-negative nonfermenters are intrinsically resistant to common antibiotics like ampicillin, most cephalosporins, and macrolides.[21,22] These bacteria, most famously *Pseudomonas aeruginosa,* are also capable of rapidly acquiring resistance to other classes of drugs, and multiple drug resistance is common.[1,10,12,21] Recent exposure to broad-spectrum antibiotics and invasive diagnostic procedures represent important risk factors for acquisition of these pathogens.[1,7,12]

P. aeruginosa is an obligate aerobic organism that is ubiquitous in the environment, particularly in decaying soil and vegetation.[2] It can be cultured from normal tissues of healthy animals, including the alimentary tract, urethra, nasal cavity, mouth, tonsils, upper airways, and conjunctivae.[2,23] Purulent exudates with a grapelike odor are characteristic. It is the epitome of an opportunistic pathogen and is rarely involved in primary disease.[12,22,23]

The pathogenesis of *Pseudomonas* infections is multifactorial and likely associated with a wide array of virulence determinants.[1,10,21,23] In animals it has been incriminated as the causative agent of many infections, including otitis, urethrocystitis, endocarditis, surgical wound infections, conjunctivitis, pneumonia, intravenous catheter site colonization, endocardial valve infections, prostatitis, and osteomyelitis.[2,23]

Most strains are resistant to chloramphenicol and retain susceptibility to amikacin.[10] The fluoroquinolones were once considered very effective for *P. aeruginosa* infections, but increasingly strains are resistant to this drug class.[21] Indeed, exposure to quinolones causes *P. aeruginosa* to develop resistance more rapidly than occurs with other bacteria.[2] The carbapenems (imipenem and meropenem) are implemented often in the treatment of MDR *P.*

aeruginosa infections.[10,21] Many strains also retain susceptibility to piperacillin-tazobactam, ticarcillin-clavulanate, and third-generation cephalosporins, particularly ceftazidime.[22] Treatment with an aminoglycoside, prescribed in combination with an antipseudomonal β-lactam, remains appropriate empiric therapy for most *P. aeruginosa* infections.[10,22] The monobactams (e.g., aztreonam) and fourth-generation cephalosporins (e.g., cefepime) are effective, albeit last-line antipseudomonal agents.[10,22,24] Appropriately, experience with both of these agents remains limited in companion animals.

Acinetobacter spp, principally *A. baumannii,* have emerged during the past few decades as one of the most difficult nosocomial microorganisms to both control and treat.[1] *Acinetobacter* spp colonize multiple sites and can persist on environmental surfaces for extended periods.[1,2,21,25] *A. baumannii* is an important cause of nosocomial pneumonia, although it is increasingly associated with other serious hospital-acquired infections.[1,2,10,25] Infections occur predominantly in select patients with risk factors such as mechanical ventilation, extended intensive care unit (ICU) stays, and prior antibiotic use.[1,2,21,25]

A. baumannii is intrinsically resistant to several classes of antibiotics.[10,12] Although carbapenems and aminoglycosides are considered the therapies of choice, *A. baumannii* strains that possess aminoglycoside-modifying enzymes and carbapenemases are increasingly reported, rendering these “last-line” antibiotics ineffective in such cases.[1,10]

Other nonfermentative gram-negative organisms implicated in hospital-acquired infections in human and veterinary medicine include *Burkholderia cepacia, Aeromonas* spp, *Chryseobacterium* spp, and *Stenotrophomonas maltophilia*. [5,10,12] These organisms survive in the environment for extended periods and are reported to cause bacteremia, meningitis, pneumonia, and urinary tract and surgical wound infections in humans and companion animals.[5,10] The increased incidence of these infections is likely a consequence of both the immunocompetence of the host and the selective pressure caused by overuse of broad-spectrum β-lactams and fluoroquinolones.[10,16,21] Prospective epidemiologic studies of infections by these pathogens are lacking in veterinary medicine.

109.7

BACTEROIDES INFECTION

Bacteroides spp are anaerobic, gram-negative bacilli or coccobacilli that, like other anaerobes, are generally opportunistic and can cause a variety of infections throughout the body. Infections involving anaerobic gram-negative bacilli arise endogenously when mucosal damage (i.e., surgery, trauma, or disease) permits tissue penetration by members of the indigenous flora.

In the bloodstream the organism can be carried to virtually any organ. Although endotoxins of *Bacteroides* are biologically impotent because they do not contain the lipid A moiety, these organisms produce several exoenzymes, including collagenase and some proteases. These enzymes are thought to play a role in the pathogenesis of the organism, assisting the bacteria in the invasion of host tissue following an initial trauma.

Bacteroides spp are among the most aerotolerant of anaerobes, able to tolerate atmospheric concentrations of oxygen for up to 3 days. During initiation of an intraabdominal infection, oxygen tolerance is believed to allow the bacteria to survive in the oxygenated tissue of the abdominal cavity until *E. coli* and other synergistic organisms are able to reduce the redox potential at the site of infection. *B. fragilis* is an important opportunistic pathogen and the most important member of the genus. It is the primary species associated with serious intraabdominal, bloodstream, bone, and wound infections and is notoriously resistant to a wide number of antibiotics. *B. fragilis* is often found in coinfections with facultative anaerobes. Importantly, however, members of the genus are not predictably susceptible to antibiotics that are considered reliable first-line or second-line drugs for infections caused by aerobic or facultatively anaerobic gram-negative pathogens. Generally effective therapies include cefoxitin, metronidazole, potentiated penicillins, and carbapenems.

109.8 RESISTANCE AMONG GRAM-NEGATIVE PATHOGENS

The frequency of antibiotic resistance is increasing dramatically, particularly among gram-negative bacteria, and antibiotics that were once formidable weapons are now commonly ineffective.* Resistance among gram-negative 471 pathogens may be due to alterations of the target binding site on the bacteria, 472 decreased penetration of the antibiotic into the bacteria, and enzymatic degradation of the target antibiotic by β-lactamases, the single most common cause of gram-negative bacterial resistance to β-lactams (see Chapter 194, Antimicrobial Use in the Critical Care Patient).[1,12,16,20]

β-Lactamases hydrolyze the β-lactam ring and render it ineffective. Plasmid-mediated β-lactamases such as those exhibited by *E. coli, K. pneumoniae,* and *B. fragilis* can generally be overcome with β-lactamase inhibitors. *P. aeruginosa, Serratia* spp and *Enterobacter* spp are chromosomal β-lactamase producers and may rapidly increase β-lactamase production if induced by penicillins or cephalosporins.

Third-generation cephalosporins were developed to circumvent β-lactam hydrolysis, but extended-spectrum β-lactamases (ESBLs) have emerged.[1,20] ESBLs, most frequently *E. coli* and *K. pneumoniae,* generally confer resistance to ceftazidime, ceftriaxone, cefotaxime, and cefepime.[20] Organisms that are inferred to have ESBLs should be reported resistant to all penicillins, cephalosporins, and aztreonam, irrespective of routine susceptibility results. However, ESBLs are not active against cephamycins (cefoxitin and cefotetan). Fluoroquinolones are often effective, although fluoroquinolone resistance is increasingly reported in human ESBL-producing pathogens. Carbapenems have retained substantial activity against β-lactamases and are presently the drugs of choice against ESBL-producing organisms, particularly when not susceptible to fluoroquinolones.[7] However, increased carbapenem use is associated with the development of resistant strains of bacteria.[8,20,21,26]

Accordingly, routine empiric prescription of the carbapenems is discouraged. Combinations of β-lactams and β-lactamase inhibitors represent an important alternative for treating infections due to susceptible ESBL-producing *Enterobacteriaceae*. Although ESBLs are recognized as an important problem in the ICU, phenotypic detection may sometimes be difficult and there is often a poor correlation with susceptibility results when published break points are applied to ESBL-producing bacteria.[1,7]

Implanted materials have significant potential for incurring biofilm infection with gram-negative pathogens.[16] Biofilms are antibiotic-resistant colonizations of bacteria that attach to surfaces and form a slimelike barrier that acts as a formidable defense mechanism, protecting the bacteria from eradication.[12,16] The biofilm matrix offers bacterial protection and thereby increases resistance to humoral immunologic responses and the phagocytic activity of host neutrophils and tissue macrophages.[16] Significantly, biofilms provide a suitable environment for the spread of resistance to several antibiotics that encode for multiple drug resistance.[16,19] In addition to rational prescription of antimicrobial agents in the ICU, a big emphasis should be placed on adequate infection control procedures to prevent transmission among hospitalized patients. It is imperative that ICUs implement a thorough disinfection protocol and have in place a means of identifying and handling patients with MDR or nosocomial infections.[1,12,16,18]

* References 1, 8, 12, 16, 20, 21.

109.9 SUGGESTIONS FOR THERAPY FOR GRAM-NEGATIVE INFECTIONS

Veterinarians are faced with the dilemma of selecting an antibiotic on two occasions during bacterial infections. Initially the clinician must prescribe empiric antibiotic coverage when the causative pathogen and its susceptibilities are unknown.[7,8] Broad-spectrum antibiotic therapy is advocated at this time for most critically ill patients with documented or suspected bacterial infections.[8,16] The term *broad spectrum* implies predictable efficacy against the most commonly encountered gram-positive and gram-negative pathogens.[7]

The second decision point occurs when the causative pathogen is identified; the transition should be made to treating the patient with the most narrow-spectrum agent once the pathogen's susceptibility profile is determined.[8] These basic tenets of pharmacotherapy are expected to reduce selective pressure for resistance to the more extended-spectrum antibiotics.[7,16]

There is considerable debate over the role of monotherapy versus combination therapy for gram-negative infections, particularly those caused by *P. aeruginosa, A. baumannii,* and the Enterobacteriaceae.[8,19,22] Combination therapy has several theoretic advantages, including in vitro bacterial killing superior to the simple additive activity of each antibiotic alone, a phenomenon termed *synergism,* as well as reducing the emergence of subpopulations of microorganisms resistant to the antibiotics.[8,22,27]

Interest in monotherapy has increased, particularly since the introduction of broad-spectrum β-lactam antibiotics effective against *P. aeruginosa.* [7,22,27] Many advantages of combining an aminoglycoside with a broad-spectrum β-lactam agent for treating gram-negative infections cannot be substantiated in the clinical setting.[27] Fluoroquinolones also demonstrate in vitro synergy with β-lactams.[28] It is important to recognize that the fluoroquinolones are not a less nephrotoxic alternative to the aminoglycosides. Although the fluoroquinolones are generally safer than aminoglycosides, the latter are predictably more effective for gram-negative pathogens and less likely to contribute to antibiotic resistance.[16,18,22,29] Moreover, not all of the veterinary-approved quinolones are sufficiently similar in their pharmacology or spectrum of activity to be used interchangeably.[17,29] Although intuitive in the critical care setting, the superiority of combination therapy has not been demonstrated conclusively in veterinary patients.

Parenterally administered antibiotics that are used frequently to treat gram-negative aerobic or facultatively anaerobic infections include the cephalosporins, aminoglycosides, fluoroquinolones, carbapenems, and ampicillin-clavulanate (Table 109-1). The first-generation cephalosporins, (e.g., cefazolin) have a spectrum of activity that includes many enteric bacteria (see Chapter 195, Penicillins and Cephalosporins). However, resistance among gram-negative bacteria develops easily, primarily by synthesis of β-lactamase enzymes capable of hydrolyzing the parent drug. Cefazolin may be prescribed appropriately for first-time, community-acquired infections by gram-negative enteric pathogens. Cefazolin is not active against *P. aeruginosa* or other opportunistic nonfermenting organisms.

The second-generation cephalosporins have some enhanced gram-negative activity when compared with the first-generation cephalosporins, but they are similarly ineffective against *P. aeruginosa*. The cephamycins, cefoxitin and cefotetan, the most frequently prescribed members of this group in veterinary medicine, are also predictably effective for most anaerobic organisms, including *B. fragilis*.

The third-generation cephalosporins are the cephalosporins that are most active against gram-negative bacteria. Among the cephalosporins, only the third-generation (ceftazidime and cefoperazone) and fourth-generation drugs (cefepime) have predictable activity against *P. aeruginosa*.

Table 109-1 Intravenous Antibiotics for Gram-Negative Infections in Dogs and Cats

Drug	Recommended Dosage
Amikacin	15 to 18 mg/kg IV q24h
Ampicillin-sulbactam	22 mg/kg IV q8h
Azithromycin	5 to 10 mg/kg IV q24h
Cefazolin	22 mg/kg IV q6-8h
Cefotaxime	25 to 50 mg/kg IV q6-8h
Cefotetan	30 mg/kg IV q8h
Cefoxitin	30 mg/kg IV q6-8h
Ceftazidime	30 mg/kg IV q6h
Enrofloxacin	15 to 20 mg/kg IV q24h (dogs) 5 mg/kg IV q24h (cats)
Gentamicin	6 to 8 mg/kg IV q24h
Imipenem-cilastatin	5 to10 mg/kg IV q6-8h
Meropenem	8 to 12 mg/kg IV q8-12h
Piperacillin-tazobactam	40 mg/kg IV q6h
Ticarcillin-clavulanate	50 mg/kg IV q6-8h
Trimethoprim-sulfamethoxazole	15 to 30 mg/kg IV q12h

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The addition of clavulanate to ampicillin enhances the parent drug's activity against some β-lactamase–producing strains of *E. coli, Klebsiella, Proteus,* and *Bacteroides* spp.[26] Ampicillin-clavulanate has little or no efficacy for *Pseudomonas, Serratia,* or *Enterobacter* spp.[26]

Imipenem and meropenem, members of the carbapenem class of β-lactam antibiotics, are among the most broadly active agents available (see Chapter 200, Miscellaneous Antibiotics) The carbapenems are used for mixed bacterial infections and gram-negative bacteria that are not susceptible to other antibiotics. Meropenem is more effective than imipenem against the *Enterobacteriaceae* and *P. aeruginosa*. [7] Both agents are active against almost all anaerobic bacteria, including all species of *B. fragilis*. Imipenem administration may be associated with CNS toxicity (e.g., seizure activity). In contrast, meropenem has a greater margin of safety. In addition, meropenem is more water soluble and thus can be administered more flexibly, as short infusions or bolus injections.

The aminoglycosides (gentamicin and amikacin) are frequently effective against gram-negative aerobic pathogens (see Chapter 196, Aminoglycosides). Amikacin is generally more active against gram-negative pathogens. Gentamicin is reportedly more nephrotoxic than amikacin. The clinical relevance of this distinction is not absolute, and both drugs have the potential to cause renal tubular injury. A high peak concentration of aminoglycoside relative to the minimum inhibitory concentration of the offending pathogen is a major determinant of clinical response. Therapy should be limited to no more than 10 days to avoid drug-associated nephrotoxicity (see Chapter 196, Aminoglycosides).

Enrofloxacin is the only approved parenteral fluoroquinolone for use in companion animals (see Chapter 197, Fluoroquinolones). However, among the fluoroquinolones, ciprofloxacin is generally more effective for MDR *P. aeruginosa* and *E. coli* infections.[17,29] Intravenous ciprofloxacin is marketed for use in human medicine, but clinical use of this formulation has not been reported in animals. Enrofloxacin is partially metabolized to ciprofloxacin, which may account for 30% to 40% of the peak fluoroquinolone concentrations.[29] There is growing concern about the emergence of resistant gram-negative bacteria associated with indiscriminate use of inappropriately low doses of fluoroquinolones.[18,21]

Colistin (polymyxin E) is a polypeptide antibiotic that has been on the market since 1950 (see Chapter 200, Miscellaneous Antibiotics). In addition to its ability to neutralize endotoxin, it is active against many gram-negative pathogens, including *P. aeruginosa, E. coli, Acinetobacter* spp, and *Stenotrophomonas maltophilia*. Its use was all but abandoned as less toxic antibiotics became available, but the emergence of MDR pathogens has prompted reevaluation in both human and veterinary patients.[1,6]

Azithromycin is a macrolide that has been used to treat specific intensive care unit infections, notably *Bordetella bronchiseptica* pneumonia (see Chapter 198, Macrolides). Empiric therapy is rarely justified, however, because many strains of *B. bronchiseptica* remain susceptible to doxycycline and fluoroquinolones (see Chapter 200, Miscellaneous Antibiotics). Although its use is increasing in veterinary medicine, there are no published reports of the applications of azithromycin in critically ill dogs or cats. Azithromycin concentrations are sustained in tissues and white blood cells, allowing for once-daily dosing. Newer classes of antimicrobial agents with activity against many MDR gram-negative pathogens include the glycylcyclines (e.g., tigecycline) and the monobactams (e.g., aztreonam)[1] (see Chapter 200, Miscellaneous Antibiotics). To curtail the development of drug resistance among our patients, veterinarians are cautioned against prescribing these agents. Consultation with a pharmacologist or veterinary microbiologist is strongly encouraged before concluding that a dog or cat requires therapy with these agents.

109.10 SUGGESTED FURTHER READING*

S Kruth: Gram negative bacterial infections. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. 2006, Saunders, St Louis, In a complete source of information on infectious diseases, this chapter presents a broad overview of the epidemiology, pathogenesis, and treatment of gram-negative infections.

MH Kollef: Gram-negative bacterial resistance: evolving patterns and treatment paradigms. *Clin Infect Dis*. **40**(2 suppl), 2005, 85, This concise summary, written by an expert in the field of ICU infections explains the importance of broad-spectrum antibiotic coverage, deescalation and surveillance strategies, as well as the application of pharmacodynamic principles in the treatment of multidrug-resistant gram-negative pneumonia.

AO Oluoch, CH Kim, RM Weisiger: Nonenteric *Escherichia coli* isolates from dogs: 674 cases (1990-1998). *J Am Vet Med Assoc*. **218**, 2001, 381, This retrospective analysis emphasizes predisposing factors and confirms the involvement of *E. coli* in a myriad of extraintestinal infections in dogs.

DM Boothe: Principles of antimicrobial therapy. *Vet Clin North Am Small Anim Pract*. **36**, 2006, 1003, The most up-to-date chapter on rational antibiotic prescribing in dogs and cats, this is a must-read for veterinarians and veterinary students. Interpretation of culture and susceptibility data and pharmacodynamic strategies to optimize therapeutic success are concisely addressed in a readily comprehensible format.

J Ogeer-Gyles, KA Mathews, P Boerlin: Nosocomial infections and antimicrobial resistance in critical care medicine. *J Vet Emerg Crit Care*. **16**, 2005, 1, This state-of-the-art review summarizes and compares data from the human and veterinary literature on antibiotic resistance in nosocomial infections, with emphasis on critically ill patients.

* See the CD-ROM for a complete list of references

110 Chapter 110 Fungal Infections

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110.1 KEY POINTS

- Fungal infections typically are slowly progressive diseases; however, respiratory, ocular, and gastrointestinal involvement can cause an emergency situation.
- Diagnosis is made most commonly with direct visualization of fungal organisms.
- Treatment includes antifungal drug therapy and supportive measures for specific organ involvement.

110.2 INTRODUCTION

Systemic fungal infections cause significant morbidity and mortality in dogs and cats in most regions of the United States. These pathogens gain entry through a single portal and disseminate to affect multiple body systems. Although affected individuals frequently present with chronic illness, fungal infections can precipitate emergency presentations for acute respiratory distress, severe gastrointestinal (GI) disease, central nervous system (CNS) disease, or acute blindness. This chapter focuses on clinical signs, diagnosis, and prognosis of the most common systemic mycoses of dogs and cats including blastomycosis, histoplasmosis, coccidiomycosis, and cryptococcosis, and will address treatment of fungal infections in general.

110.3 BLASTOMYCOSIS

Blastomycosis is caused by infection with fungal spores of *Blastomyces dermatitidis,* most commonly via inhalation and respiratory colonization. Environmental conditions favoring fungal growth include moist, acidic soil with decaying vegetation or animal feces. Geographic regions with the greatest prevalence of blastomycosis include the Mississippi, Missouri, and Ohio River valleys and the Great Lakes areas of the United States and Canada.[1]

Infection typically occurs when an animal inhales conidiophores from the environment, but inoculation by penetration can cause localized disease. Dogs are affected more commonly than cats.[1,2] Following inhalation, infective conidia are phagocytized by macrophages and transformed to the thick-walled yeast phase (8 to 12 μm) that bud to form daughter cells with broad-based attachments (Color Plate 110-1, *A*). Yeast may produce a localized infection or may disseminate to distant sites.[3]

110.3.1 Clinical Signs

Affected dogs are typically young adult, large breed, and of either gender.[4] Clinical signs develop weeks to months after exposure to the organism and include anorexia, depression, lethargy, weight loss, cachexia, and fever. Physical examination findings include respiratory signs (tachypnea, dyspnea, cyanosis, respiratory distress, pulmonary thromboembolism), lymphadenopathy, ocular changes (uveitis, retinal detachment, secondary glaucoma), dermal nodules, bone lesions, and CNS abnormalities.[1,3-5] Pyogranulomatous inflammation occurs as a result of stimulation of cell-mediated immunity.[3]

Blastomycosis is an uncommon fungal disease in cats.[2] Clinical signs are similar to those in dogs, except cats more commonly exhibit CNS disease and develop large dermal abscesses.[2,3]

110.3.2 Diagnosis

Complete blood count (CBC) may reveal mild nonregenerative anemia, mature neutrophilia, or neutrophilia with left shift. Possible abnormalities on serum biochemical profile include hypoalbuminemia, hyperglobulinemia, and hypercalcemia.[1,4] Thoracic radiographs reveal a diffuse or nodular interstitial pattern, alveolar infiltrates, hilar lymphadenopathy, or a combination of these in 70% of cases. Bone involvement most commonly affects the appendicular skeleton. Radiographic lesions (osteolysis with periosteal proliferation and soft tissue swelling) are similar to those seen in primary osteosarcoma.[1,3,4]

Definitive diagnosis relies on identifying organisms retrieved from affected sites. The site of involvement dictates the method of sampling. Aspirating affected lymph nodes, dermal lesions, or eyes (vitreous) yields organisms reliably. Lung aspirate, tracheal wash, and bronchoalveolar lavage (BAL) are frequently nondiagnostic because of the interstitial location of the organisms.[4] Culture is unnecessary if cytologic or histopathologic examination demonstrates characteristic organisms. Caution should be exercised when handling infected tissues because the yeast form is infective to humans.[1]

Serologic testing should be considered when multiple attempts to identify the organism have failed. Agar gel immunodiffusion (AGID) is the serologic test most commonly used to identify antibodies to *Blastomyces* organisms, with sensitivity reported to be 41% to 90%, and specificity of 90% to 100%.[6,7] AGID is often negative early in the course of disease and may remain positive even with clinical resolution of disease. AGID in cats is unrewarding.[2]

Antigen testing for *Blastomyces dermatitidis* has become available (MiraVista Diagnostics, Indianapolis, IN).[8] This test in an enzyme immunoassay that can be performed on serum or urine from affected dogs, has greater sensitivity (serum sensitivity 87%, urine sensitivity 93%) than antibody testing, and appears to have a low rate of false-positive results in uninfected dogs.[8]

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110.3.3 Prognosis

The prognosis of a patient with blastomycosis is generally good unless there is CNS or severe pulmonary involvement.[1] Approximately 70% to 75% of dogs receiving antifungal therapy survive. Dogs with severe respiratory infections or multiple body system involvement are more likely to die within the first week of therapy. Brain involvement is associated significantly with treatment failure. Most animals that die during or soon after treatment do so because of the subsequent inflammatory response associated with sudden death of many fungal organisms.

110.4 HISTOPLASMOSIS

Histoplasmosis is caused by infection with the soil-borne, dimorphic fungus *Histoplasma capsulatum*. This organism survives wide temperature variations. Moist soil containing bird or bat waste favors growth. Regions of the United States with greatest prevalence are the Ohio, Missouri, and Mississippi river valleys.[9-11]

Soil contaminated with *Histoplasma capsulatum* contains free-living microconidia (2 to 5 μm) or macroconidia (5 to 18 μm) that cause mammalian infection. Route of entry is typically respiratory; however, oral exposure may occur because some animals have only GI signs.[10] Dissemination occurs to any organ. Lungs, GI tract, lymph nodes, spleen, liver, bone marrow, eyes, and adrenal glands are most commonly affected. The incubation period is 12 to 16 days in dogs, but clinical signs may be absent or insidious.[3] Exposure to highly contaminated environments may cause point-source outbreaks in dogs and humans. Cats and dogs are equally likely to develop histoplasmosis.[11]

110.4.1 Clinical Signs

Most affected dogs are large breed, young adults. Males are slightly predisposed, and hunting breeds are overrepresented.[3,10] Disseminated histoplasmosis with GI involvement accounts for most clinical presentations.[11] GI signs include both small and large intestinal diarrhea, weight loss, hypoalbuminemia, intestinal bleeding (melena or hematochezia), and tenesmus. Hepatosplenomegaly occurs in up to 50% of dogs. Coughing, tachypnea, dyspnea, or pleural effusion occurs with pulmonary involvement. Less specific findings include fever, anorexia, and depression. In contrast to blastomycosis, histoplasmosis is less frequently associated with bone, ocular, or dermal lesions.[11]

Cats with histoplasmosis have slightly different clinical signs than dogs. Cats younger than 4 years are affected most commonly, with no breed or gender predilection.[9,11] Clinical signs include weight loss, depression, fever, anorexia, and anemia. Specific GI signs are identified less commonly. Pulmonary involvement results in dyspnea, tachypnea, and abnormal lung sounds. Lymphadenopathy and hepatosplenomegaly occur with dissemination. Bone marrow involvement can cause various blood cell deficiencies. Dermal, ocular, and oral lesions occur uncommonly.

110.4.2 Diagnosis

There are no pathognomonic findings on routine laboratory evaluation consistent with histoplasmosis. Nonregenerative anemia is the most common CBC abnormality, occurring as a result of chronic inflammation, GI blood loss, and bone marrow infection.[3] Thrombocytopenia commonly occurs. Serum biochemical profile abnormalities include hypoalbuminemia, elevated hepatic enzymes and total bilirubin, and hypercalcemia.[3] Thoracic radiographs reveal diffuse or nodular interstitial infiltrates, or hilar lymphadenopathy.[11]

Definitive diagnosis is established by identification of *Histoplasma capsulatum* via cytology or histopathology. Organisms typically are found clustered within mononuclear phagocytes. *Histoplasma capsulatum* organisms are 2 to 4 μm in diameter, with a thin, clear halo surrounding basophilic cytoplasm (Color Plate 110-1, *B*). Diagnostic samples may be obtained from rectal mucosal scraping, lymph node aspirate, dermal nodule cytology, bone marrow, liver or splenic aspirate, or BAL.

Serologic tests to diagnose histoplasmosis are unreliable, with both false-negative results occurring in active disease and false-positive results occurring in animals without active disease. Serum antibody testing (AGID, complement fixation) is available for identification of histoplasmosis in companion animals; however, results are unreliable, with frequent false-positive and false-negative results.[12] Antigen detection testing is available for humans (MiraVista Diagnostics, Indianapolis, IN).[12] Further testing is needed to evaluate the usefulness of this diagnostic method for dogs and cats.

110.4.3 Prognosis

Statistics on mortality with histoplasmosis have not been reported for dogs since the advent of itraconazole therapy. In one report, eight cats that had failed initial treatment with ketoconazole were cured with itraconazole.[12] In the author's experience, prognosis is guarded to good depending on the nature of systemic involvement of organ systems.

110.5 COCCIDIOIDOMYCOSIS

Coccidioidomycosis is a systemic fungal infection caused by *Coccidioides immitis,* a soil saprophyte that grows in semiarid conditions. Growth of *C. immitis* is limited to the southwestern United States, Mexico, and Central and South America.[3,13] In the environment, *C. immitis* grows as a mycelium with thick-walled, barrel-shaped arthroconidia, 2 to 4 μm wide and 3 to 10 μm long. Following exposure by inhalation, the arthroconidia form a spherule 20 to 200 μm in diameter. The disease has been reported in most mammals, but dogs are infected more frequently than cats.[13]

Exposure and infection occur via the respiratory route.[11] Inhaled arthrospores migrate through the pleural tissue to the subpleural space. The incubation period ranges from 1 to 3 weeks in dogs. An intense inflammatory response develops, causing clinical respiratory signs. If dissemination occurs, involvement of other organ systems includes bones, eyes, heart, pericardium, testicles, brain, spinal cord, and visceral organs.[11]

110.5.1 Clinical Signs

Young adult, large breed outdoor dogs are predisposed to these infections.[3] Clinical signs primarily occur in the respiratory system and may be unapparent following exposure. In animals with ineffective immunity, signs become severe. Chronic cough is the most common initial complaint. Fever, weight loss, and anorexia are also common.[3,13] Bone involvement occurs in 65% of dogs, sometimes causing draining skin nodules over bone lesions.[3] Myocardial or pericardial infection causes cardiac arrhythmias or restrictive pericarditis.[13] CNS signs include seizures, behavior change, or coma. Ocular involvement is less common with coccidioidomycosis than with other systemic fungal infections.[5]

Cats are resistant to coccidiodmycosis compared with dogs.[14] There is no obvious age, breed, or gender predilection. Skin lesions from dermal inoculation with fungus are the most common manifestation. Lesions may form masses or be associated with abscess formation and drainage.[14] Fever, inappetence, and weight loss commonly occur in affected cats. Respiratory signs occur in only 25% of affected cats.[14]

110.5.2 Diagnosis

Changes on CBC include normocytic, normochromic, nonregenerative anemia, neutrophilia, plus or minus left shift, and monocytosis. Serum biochemical profile commonly reveals hypoalbuminemia and hyperglobulinemia, hepatic transaminases elevation, and azotemia. Hypercalcemia can occur.

Thoracic radiographs reveal a diffuse interstitial or peribronchial pattern, frequently with hilar lymphadenopathy. Alveolar infiltrate can occur. Pleural involvement includes pleural thickening, effusion, and fibrosis. Hypertrophic osteopathy has been reported with pulmonary involvement.[13]

Demonstration of organisms provides a conclusive diagnosis for coccidioidomycosis. Locating organisms is often difficult because of relatively low organism numbers and difficulty obtaining samples from inaccessible locations.[3,13] Fungal culture is not clinically useful, because definitive identification requires inoculation into animals to induce spherule formation.

Serologic diagnosis of coccidioidomycosis often is used when organisms are not found. A variety of serologic tests may be used to detect immunoglobulin M and immunoglobulin G antibodies. Serologic testing should be interpreted in light of signs consistent with active infection to confirm diagnosis. It is possible to obtain negative serologic results in affected animals. Repeat testing in 2 to 4 weeks to demonstrate increasing titer is warranted in questionable cases.[13]

110.5.3 Prognosis

Coccidioidomycosis remains a challenge to treat, and it is difficult to cure compared with other systemic mycoses. Localized respiratory infections may resolve spontaneously and generally carry a good prognosis. Disseminated infections will result in death if not treated. An overall recovery rate of 60% has been noted with ketoconazole therapy; however, multiple bone or CNS involvement carries a worse prognosis.[13]

110.6 CRYPTOCOCCOSIS

Cryptococcosis is caused by a variety of species of *Cryptococcus,* with *C. neoformans* being the most clinically significant because it thrives at mammalian body temperature. *Cryptococcus* is a saprophytic, round, yeastlike fungus 3.5 to 7 μm in diameter, with a capsule of 1 to 30 μm that does not take up cytologic stains.[15] *Cryptococcus* reproduces by budding from the parent cell. Buds can break off at different stages of growth, resulting in size variation of organisms (Color Plate 110-1, *C*). Environmental sources are near avian habitats or in litter of eucalyptus trees. Cryptococcosis does not occur in a defined geographic region.[16]

Cryptococcosis occurs with greater frequency in cats than in dogs.[16] The most likely route for infection is the respiratory tract. *Cryptococcus* is unencapsulated in the environment and may be as small as 1 μm, enhancing respiratory colonization. Following tissue deposition, organisms colonize either the upper or lower respiratory tract and regenerate their capsules. The capsule prevents normal host immune response and organism elimination. CNS involvement is common in both cats and dogs and may occur as a result of extension from nasal cavity disease.[16-19]

110.6.1 Clinical Signs

Cryptococcosis is the most common systemic fungal infection of cats. There is no obvious gender predilection and age range of infection is broad.[16] Upper respiratory infection is evident in 50% to 60 % of cases.[15] Clinical signs include nasal or facial deformity, mass protruding from nares, nasal discharge, skin lesions, sneezing, respiratory noise, or change of voice. Ocular and CNS signs occur in approximately 15% of cases. Ocular signs consist of blindness due to retinal detachment and granulomatous chorioretinitis.[20] Neurologic signs include depression, temperament changes, ataxia, vestibular signs, and blindness.[16,21]

Affected dogs are generally less than 4 years of age. Great Danes, Doberman Pinschers, Labrador Retrievers, and American Cocker Spaniels are overrepresented.[3] Clinical signs most often are localized to the CNS, with seizure, ataxia, central vestibular disease, papilledema, cervical pain, tetraparesis, or multifocal cranial nerve involvement.[18] Dogs may also have ocular lesions to include granulomatous chorioretinitis, retinal hemorrhage, and optic neuritis.[5]

110.6.2 Diagnosis

Results of CBC and serum biochemical profile are usually unremarkable. Thoracic radiographs occasionally reveal nodular interstitial infiltrates, hilar lymphadenopathy, or pleural effusion. Skull radiographs or computed tomography can demonstrate nasal bone destruction and soft tissue swelling.[3] With CNS involvement, cerebrospinal fluid commonly exhibits increased protein and mixed mononuclear and neutrophilic pleocytosis.[18]

The most reliable method to diagnose cryptococcosis is direct organism visualization on cytologic or histopathologic evaluation (Color Plate 110-1, *D*). Cytologic examination may be performed on nasal discharge, skin exudates, cerebrospinal fluid, tissue aspirate, or samples obtained by ocular paracentesis. Dogs may have subclinical renal infection; therefore microscopic evaluation of urine sediment is warranted. Wright stain may cause some distortion of *Cryptococcus* spp and Gram stain may facilitate visualization.

Serologic testing is available and useful to aid diagnosis. Recommended testing consists of latex agglutination testing to identify capsular antigen. Antigen testing is considered positive at a titer of 1:16 or greater. Response to treatment is correlated with declining titer results. Testing cerebrospinal fluid for cryptococcal antigen can confirm diagnosis with CNS involvement when the organism cannot be visualized.[17] 476 477

Histopathology of affected tissue is indicated if cytology results are negative; however, impression smears should always be made of biopsy samples because of the comparative ease of cytologic diagnosis. Histopathologically, the large capsule differentiates *Cryptococcus* from *Blastomyces,* and budding and lack of endospores differentiate it from *Coccidioides immitis*. Fungal isolation is not clinically useful because of prolonged growing time.

110.6.3 Prognosis

Cats have a good prognosis when disease occurs outside of the CNS.[17] Progressive decrease of antigen titer by 10-fold over 2 months has been associated with favorable prognosis in cats. Dogs with any form of disease, and cats with CNS disease, have a guarded prognosis.[17] In cats, concurrent feline leukemia virus and feline immunodeficiency virus infections decrease response to treatment.

110.7 TREATMENT

In general, treatment for fungal infections can be separated into definitive antifungal therapy for long-term control or cure of the disease and supportive care to minimize the acute signs associated with specific organ involvement. There are a limited number of antifungal drugs and treatment regimens, which will be discussed in detail in Chapter 199, Antifungal Therapy.

110.7.1 Respiratory Supportive Therapy

Respiratory decompensation is the most common reason for emergency presentation of fungal disease. Although any fungal organism can cause respiratory infection, blastomycosis is the most common pulmonary fungal pathogen, followed by coccidioidomycosis and histoplasmosis. Supportive therapy for hypoxemic patients includes supplemental oxygen. Respiratory rate, effort, and oxygenation status (arterial blood gas, pulse oximetry) should be monitored as frequently as needed to address patient changes. Respiratory arrest can occur with severe infection, necessitating cardiopulmonary resuscitation and mechanical ventilation. Pulmonary thromboembolism has been reported with fungal infections and would cause acute deterioration in respiratory function. Antibiotics can be prescribed if secondary bacterial infection is suspected.[1] Handling should be kept to a minimum to reduce stress-induced respiratory effort. Short-term antiinflammatory glucocorticoids have been advocated when initiating antifungal chemotherapy in patients with respiratory compromise to minimize the effects of rapid fungal death and subsequent inflammatory response.[22,23]

110.7.2 Gastrointestinal Supportive Therapy

Histoplasmosis is the fungal pathogen that most commonly affects the GI tract, causing signs consistent with small or large bowel diarrhea. Ancillary therapy includes dietary modification and antibiotic therapy to control concurrent small intestinal bacterial overgrowth. Antidiarrheal therapy may be helpful in conjunction with antifungal therapy for symptomatic relief.[3,11] Loss of body condition is often dramatic as a result of prolonged anorexia, malabsorption, and malnutrition, and affected animals are often debilitated at the time of diagnosis. Partial or total parenteral nutrition support can be prescribed until normal GI function resumes. With severe intestinal disease, GI absorption of oral antifungal medications might not occur normally, causing treatment failure.

110.7.3 Ocular Supportive Therapy

Fungal ocular infection causes moderate to marked bilateral uveitis, with secondary glaucoma in some instances. Retinal detachment is common with fungal disease, and permanent vision loss can result. Ocular changes are associated with pain and discomfort. Ancillary therapy for uveitis or glaucoma can be prescribed, to include topical glucocorticoids and carbonic anhydrase inhibitors as needed.[5] Enucleation may be recommended in blind, painful eyes, and histopathology can be performed on the tissue for definitive diagnosis if not yet established.

110.7.4 Other Supportive Therapy

Orthopedic pain from bone lesions can be treated with nonsteroidal antiinflammatory medications pending resolution of infection. Dermal wounds should be shaved and kept clean and dry. Personnel who handle animals with draining wounds should exercise caution to avoid accidental infection.[24]

110.8 SUGGESTED FURTHER READING*

KA Arceneaux, J Taboada, G Hosgood: Blastomycosis in dogs: 115 cases (1980-1995). *J Am Vet Med Assoc*. **213**, 1998, 658, *Study that includes cases collected over a 15-year period in the southeastern United States; describes diagnostic tests performed, treatment administered, and outcome in a retrospective format*.

CF Berthelin, CS Bailey, PH Kass, et al.: Cryptococcosis of the nervous system in dogs. 1. Epidemiologic, clinical, and neuropathologic features. *Prog Vet Neurol*. **5**, 1994, 88, *First of a series of articles that provides a thorough description of neurologic manifestations of CNS cryptococcosis in dogs*.

RT Greene: Coccidiomycosis. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. ed 3, 2006, Elsevier, St Louis, *A chapter that provides a thorough review and update for coccidiomycosis in cats and dogs*.

RD Hodges, AM Legendre, LG Adams, et al.: Itraconazole for the treatment of histoplasmosis in cats. *J Vet Intern Med*. **8**, 1994, 409, *A retrospective case series that identifies itraconazole (FDA approved for use in 1992) as the treatment of choice for histoplasmosis in cats*.

RL Schulman, BC McKiernan, DJ Schaeffer: Use of corticosteroids for treating dogs with airway obstruction secondary to hilar lymphadenopathy caused by chronic histoplasmosis: 16 cases (1979-1997). *J Am Vet Med Assoc*. **214**, 1999, 1345, *An article that reviews ancillary treatment with glucocorticoids to manage hilar lymphadenopathy, a particularly frustrating complication of fungal disease*.

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* See the CD-ROM for a complete list of references

111 Chapter 111 Viral Infections

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111.1 KEY POINTS

- A number of viral infections may be associated with acute and severe illness leading to presentation of affected dogs and cats to emergency and critical care veterinarians.
- Treatment of viral infections is generally supportive and symptomatic and includes intravenous fluid therapy, early nutrition, antiemetic therapy, oxygen therapy, and antibiotics for secondary bacterial infections. Hospitalization in isolation may be required.
- The feline leukemia virus and feline immunodeficiency virus status of all cats should be known.
- The use of antiviral medications is limited, and there are few controlled studies evaluating their effectiveness in dogs and cats.
- The range of diagnostic tests for viral infections in dogs and cats has increased with the availability of nucleic acid–based assays, such as the polymerase chain reaction (PCR). Quality control for PCR assays can be problematic, so the veterinarian should contact the laboratory to ensure adequate positive and negative controls have been included; refereed publications regarding validation of a specific laboratory's assay(s) should also be sought.

111.2 INTRODUCTION

A large number of viruses may cause acute and severe illness in dogs and cats (Table 111-1). The most common or important viral infections that may come to the attention of emergency and critical care veterinarians are canine parvovirus (CPV), canine distemper virus (CDV), canine influenza virus, feline panleukopenia virus, feline herpesvirus (FHV-1), feline calicivirus (FCV), feline infectious peritonitis virus (FIPV), feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), and rabies virus infection. The FIV and FeLV status of all cats should be determined on arrival by questioning the owner or testing using in-house enzyme-linked immunosorbent assays for FeLV antigen and FIV antibody. Because these infections may be detected in asymptomatic cats, and because some cats may eliminate FeLV, positive test results alone are not reason for euthanasia. CPV infection is covered in the following chapter. Other viral diseases that may present to emergency and critical care veterinarians include enteric viral infections such as rotavirus and coronavirus infections, feline paramyxovirus infection, pseudorabies virus infection, vector-borne viral infections such as West Nile virus infection, infectious canine viral hepatitis, and canine herpesvirus infection.

An extensive discussion of the etiology, clinical signs, diagnosis, treatment, and prevention of every one of these infections is beyond the scope of this chapter. Instead, the purpose of this chapter is to provide the reader with an update on selected common and important viral infections in dogs and cats that may present to emergency and critical care veterinarians. Treatment of viral infections is largely supportive and symptomatic and usually includes intravenous fluid therapy, early enteral or parenteral nutrition, antiemetics, analgesia, and oxygen therapy when pulmonary disease is present. Blood products may be needed for cats with retroviral infections. Antibiotics may be needed for secondary bacterial infections. Attempts to culture secondary bacterial invaders and determine sensitivity to antimicrobial agents should be considered before commencing antimicrobial therapy. Use of antiviral medications is still limited in dogs and cats, and controlled studies are lacking.

111.3 CANINE DISTEMPER VIRUS INFECTION

CDV infection is a contagious disease of dogs that may involve the gastrointestinal (GI), respiratory, or neurologic systems. Distemper still occurs sporadically, even in vaccinated dog populations. Disease most commonly occurs in dogs 3 to 6 months of age, when maternal antibody level is declining, but can occur in older dogs that have been vaccinated infrequently, especially following stress, immunosuppression, or contact with other affected dogs.[1]

CDV is an enveloped ribonucleic acid (RNA) virus that belongs to the family Paramyxoviridae. The virus survives for about 3 hours at room temperature and is highly susceptible to routine hospital disinfectants such as quaternary ammonium compounds. Several strains of CDV exist and vary in pathogenicity. Some, such as the Snyder Hill strain, are more likely to produce neurologic disease than others. A study has documented the existence of CDV strains that differ from vaccine strains and those previously documented in the United States.[2]

CDV is shed in respiratory secretions for up to 90 days after infection. Initial replication of CDV is in lymphoid tissue, and viral destruction of lymphocytes results in lymphopenia and pyrexia. Approximately 1 week after infection the virus spreads to epithelial tissues (lungs, GI tract, kidney, bladder) and the central nervous system (CNS), and virus shedding begins. Poor cell-mediated immunity (CMI) is associated with spread of the virus to a variety of tissues, severe respiratory and GI signs with or without CNS involvement, and death. Dogs with an intermediate or delayed CMI response may develop persistent infection of the uvea, CNS, and footpad and nasal epithelium, leading to neurologic, cutaneous (hard pad), and ocular signs such as chorioretinitis. Infection with CDV is highly immunosuppressive, and secondary infections with opportunistic organisms such as *Toxoplasma* and *Salmonella* may occur.

Distemper should be high on the list of differential diagnoses for any dog with respiratory and/or CNS signs. Mild signs are common and resemble those of kennel cough. Severe, generalized distemper may begin with a serous to mucopurulent conjunctivitis and rhinitis, and progress to include signs of lower respiratory disease, depression, anorexia, vomiting and diarrhea, severe dehydration, and death. Neurologic signs then occur in some dogs, either with systemic illness or after a several-week delay. Neurologic signs are frequently progressive despite treatment and are a poor prognostic sign. Myoclonus, an involuntary twitching of various muscle groups, can be most pronounced when affected dogs are resting and is virtually pathognomonic for CDV infection. Ocular signs may consist of sudden blindness due to optic neuritis, chorioretinitis, or retinal detachment. Cutaneous signs may be useful for prognostication. Footpad and nasal hyperkeratosis often are accompanied by neurologic complications, whereas the presence of vesicular and pustular dermatitis implies a good CMI response and rarely is associated with neurologic complications.

Table 111-1 Viral Infections To Be Included on the List of Differential Diagnosis in Dogs and Cats With Respiratory, Gastrointestinal, or Neurologic Symptoms

	Affected Body System		
Species	**Respiratory**	**Gastrointestinal**	**Neurologic**
Dog	Canine distemper Canine influenza Canine parainfluenza Canine adenovirus Canine herpesvirus	Canine distemper Canine parvovirus Canine coronavirus Rotavirus	Canine distemper Rabies Arthropod-borne infections (togaviruses, bunyaviruses, and flaviviruses)[*]
Cat	Feline calicivirus Feline herpesvirus Feline infectious peritonitis Retroviruses[†]	Feline panleukopenia Feline enteric coronavirus Rotavirus Feline infectious peritonitis Retroviruses[†]	Feline panleukopenia Feline infectious peritonitis Rabies FIV Retroviruses[†] Paramyxoviruses

FIV, Feline immunodeficiency virus.

Physical examination of dogs suspected to have distemper should include a fundic examination, careful inspection of the skin, including the nose and footpads, and careful thoracic auscultation. Any dog suspected to have distemper should be placed in isolation if possible. This may be complicated by a requirement for oxygen therapy.

The most commonly used diagnostic test for distemper is cytologic examination of conjunctival scrapings. Acutely, these may show cytoplasmic inclusions in epithelial cells when stained with Wright or Diff-Quik stain (Color Plate 111-1). The sensitivity of cytology is increased following application of immunofluorescent antibody to smears by regional diagnostic laboratories. Smears should be air dried and, if possible, fixed in acetone for 5 minutes before transport. Intracytoplasmic inclusions may also be seen in erythrocytes, lymphocytes, other white blood cells, and cells within the cerebrospinal fluid (CSF). Thoracic radiography may reveal an interstitial pattern, or an alveolar pattern with secondary bacterial bronchopneumonia. Analysis of CSF may show increased protein and cell count, and measurement of anti-CDV antibody in the CSF can also be useful for diagnosis in dogs with neurologic signs. Other antemortem diagnostic tests for distemper include immunohistochemistry for CDV antigen on biopsies of nasal mucosa, footpad epithelium, and haired skin of the dorsal neck, and reverse transcriptase–polymerase chain reaction (RT-PCR) testing for viral nucleic acid. Samples suitable for RT-PCR testing include buffy coat cells, whole blood, serum, CSF, and urine.[3] With any PCR assay, quality control can be problematic, and the laboratory should be consulted to ensure adequate positive and negative controls are included. Virus isolation is difficult and is not widely used for diagnosis.

Modified live vaccines can prevent canine distemper and should provide at least partial protection even in the face of variant strains. The interested reader is referred to a comprehensive review of vaccination for CDV for further information on the topic.[1]

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[*] These also have the potential to cause disease in cats, but dogs are most commonly affected.

[†] Feline retrovirus infections may also be associated with these signs through induction of neoplastic disease or secondary infections resulting from immunosuppression.

111.4 CANINE INFLUENZA VIRUS INFECTION

Canine influenza first appeared in racing Greyhounds in Florida between 1999 and 2003.[4] At the time of writing, antibodies to canine influenza virus have been detected in dogs in animal shelters, adoption groups, pet stores, boarding kennels, and veterinary clinics in 19 U.S. states.[5] Sequence analysis has indicated that the virus isolated from dogs shares more than 96% homology with equine influenza A. All the genes from the canine isolates are of equine influenza virus origin, providing evidence that the virus crossed the species barrier. There is concern that this virus may also cross the dog-human species barrier, as occurs with avian influenza viruses. Influenza viruses are enveloped viruses that are susceptible to routine hospital disinfection practices.

Signs occur 2 to 5 days after exposure to the virus. As with distemper, canine influenza virus causes a syndrome that may mimic kennel cough, although fever may be more likely to occur with influenza virus than with parainfluenza virus, adenovirus, and *Bordetella bronchiseptica*. Nearly 80% of exposed dogs develop clinical signs, which consist of a cough that persists for 2 to 3 weeks despite therapy, serous to mucopurulent nasal discharge, and a low-grade fever. Some dogs may develop more severe pneumonia with a high fever (104° to 106° F), tachypnea, and dyspnea. The overall mortality has been less than 5%. Shedding of virus occurs for 7 to 10 days after the onset of clinical signs. 479 480

Dogs with these signs should be placed in isolation. Findings on thoracic radiography are the same as those described above for distemper. Antemortem diagnosis of canine influenza virus infection relies on serology using hemagglutination inhibition, RT-PCR, or virus isolation. In order to distinguish past exposure from recent infection, serology should be performed on samples collected at the time of presentation and 2 to 3 weeks later. Because most dogs have not yet been exposed, positive results in a single sample collected 7 days after onset of clinical signs may be suggestive of current infection.

Nucleic acid testing using RT-PCR is offered by a few laboratories and can be performed on pharyngeal swabs. Pharyngeal swabs should be kept refrigerated and transported as soon as possible on ice to the laboratory performing nucleic acid testing. Detection of virus appears to be difficult beyond 3 to 4 days after the onset of clinical signs; the same is true for virus isolation.[5] Virus isolation and RT-PCR can also be successful when performed on lung tissue from dogs that have died within 2 to 3 days of the onset of clinical signs. Swabs for virus isolation must be placed in virus transport medium.

Treatment of serious influenza virus infection in human patients has involved use of the neuraminidase inhibitor oseltamivir phosphate, which inhibits spread of the virus from cell to cell.[6] Anecdotal reports exist regarding treatment of dogs with this drug, but no published studies are available, and nothing is known regarding the optimal dosage in dogs to inhibit viral replication. Until the results of such studies become available, use of this drug to treat dogs that have been definitively diagnosed with canine influenza virus infection is not recommended.

111.5 FELINE PANLEUKOPENIA

Feline panleukopenia is caused by a small, single-stranded deoxyribonucleic acid (DNA) virus that is closely related to CPV. Cats with feline panleukopenia may also be infected with CPV strains 2a and 2b.[7] Although most cats shed virus for just a few days after infection, it may be shed for as long as 6 weeks, and viral persistence in the environment plays an important role in disease transmission. The virus can survive for a year at room temperature on fomites and survives disinfection with routine hospital disinfectants; inactivation generally requires bleach solution (6% sodium hypochlorite).

Feline panleukopenia should be suspected in poorly vaccinated kittens with acute illness including fever, depression, anorexia, vomiting and, less commonly, diarrhea. Oral ulceration and icterus may be noted in complicated infections. Death may result from severe dehydration, secondary bacterial infections, and disseminated intravascular coagulation. Cats between 3 and 5 months of age may be most susceptible to severe disease, which is exacerbated by concurrent gastrointestinal infections.

Cats suspected to have feline panleukopenia should be placed in isolation. Supportive treatment is similar to that recommended for CPV. Diagnosis is based on clinical signs along with the finding of leukopenia on a complete blood count. Leukopenia is not always present and may occur with other diseases such as salmonellosis. Severe panleukopenia may be associated with concurrent infection with FeLV.[8] In-house fecal enzyme-linked immunosorbent assays for CPV are suitable for diagnosis of feline panleukopenia, although false-negative results may occur, so a negative test result does not rule out feline panleukopenia. PCR assays are also available for detection of viral DNA in fecal and tissue samples from affected cats.

111.6 FELINE RESPIRATORY VIRAL DISEASE

The most common causes of feline respiratory viral disease are FHV-1 and FCV. FHV-1 is an enveloped DNA virus. It survives a maximum of 1 day at room temperature and is susceptible to destruction by common disinfectants. FCV is a nonenveloped RNA virus, which survives up to 10 days at room temperature. Inactivation requires hypochlorite solutions; quaternary ammonium compounds are not effective.[9]

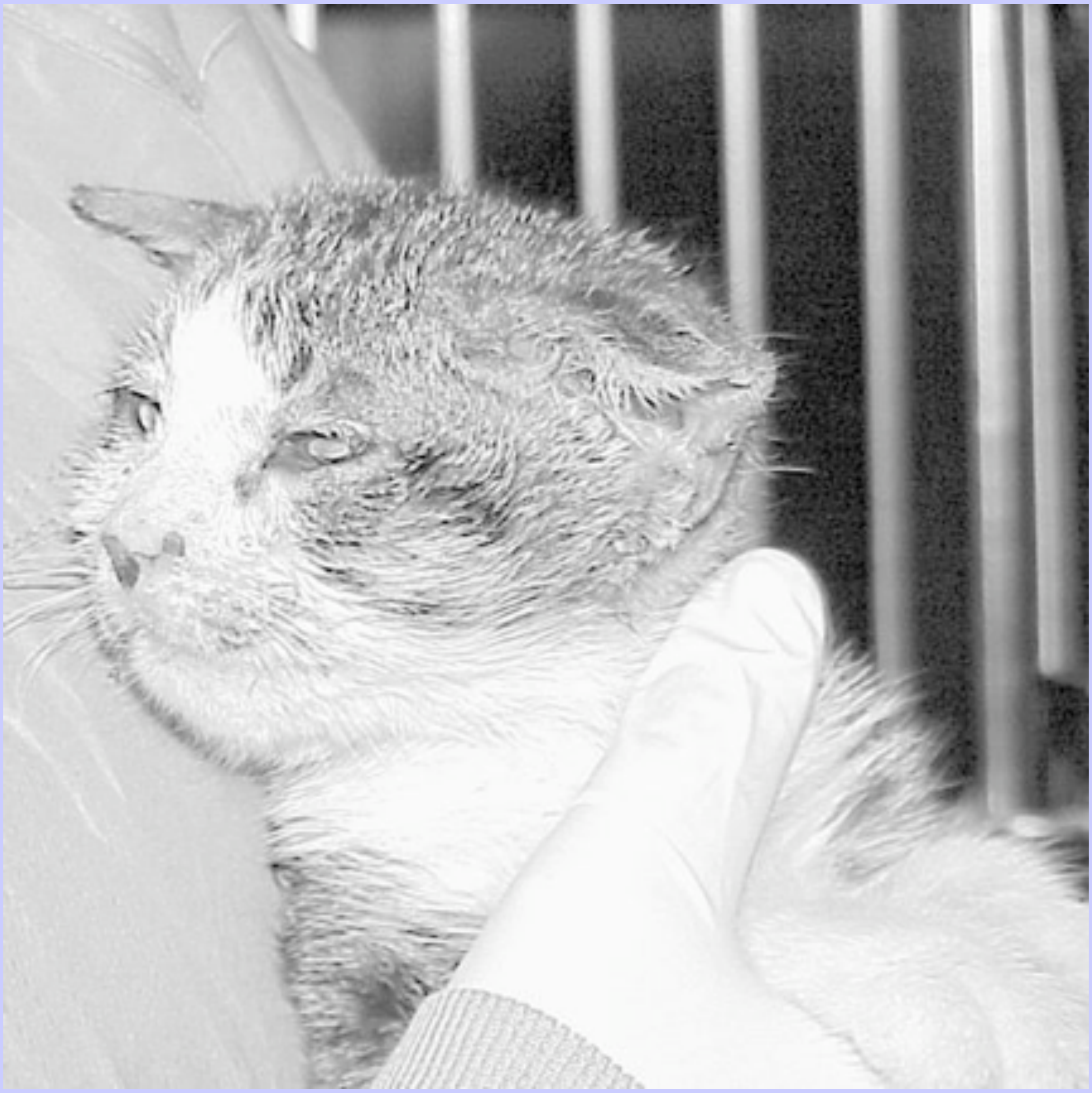
FHV-1 and FCV infections may be acquired by contact with acutely infected cats, contact with organisms in the environment, or by contact with carrier cats. The chance of infection is increased when large numbers of cats are housed together. Both viruses replicate mainly in the tonsils and respiratory tissues. In addition to the nasal, conjunctival, and oral shedding common to both viruses, FCV is also shed in the feces and occasionally in the urine.

Almost all cats infected with FHV-1 develop latent infections, whereby the virus persists in tissues such as the trigeminal ganglia for the life of the animal. Reactivation of virus shedding occurs in roughly 50% of infected cats, with or without concurrent clinical signs. This may occur spontaneously or following stressful events. Shedding occurs 4 to 11 days after the stress and lasts 1 to 2 weeks. In contrast, shedding of FCV by persistently infected cats is continuous and not affected by stress. In some cats, shedding is lifelong; in others, it ceases after several weeks.

Acute disease caused by FCV and FHV-1 occurs after an incubation period of 2 to 10 days. The most severe signs tend to occur in very young and elderly debilitated cats. Concurrent immunosuppressive illness or infection with other respiratory pathogens and opportunistic bacteria can dramatically influence the severity of disease. Clinical signs common to both infections include conjunctivitis, serous or mucopurulent nasal discharge and sneezing and, less commonly, coughing and dyspnea. Depression, anorexia, hypersalivation, and pyrexia may also be present in acute infections. FHV-1, but not FCV, may be associated with corneal ulceration and keratitis. Ulcerative glossitis is more common and severe with FCV infection but may be associated with FHV-1 infection. A small proportion of FCV carriers develop chronic lymphoplasmacytic or chronic ulceroproliferative stomatitis, which is often refractory to therapy. Transient lameness and pyrexia have been reported in association with acute FCV infection and following FCV vaccination.

Highly virulent strains of FCV have been isolated from outbreaks of severe systemic febrile illness.[10,11] This condition is characterized by a high mortality, fever, anorexia, ulcerative facial dermatitis, and diffuse cutaneous edema (Figure 111-1). Several cats developed coagulopathies, along with hypoproteinemia and mild hyperbilirubinemia. The suspected or confirmed outbreaks of infection reported shared several significant features: (1) in every outbreak where a suspected index case was identified, a hospitalized shelter cat appeared to be the source of infection, (2) otherwise healthy, adult, vaccinated cats were prominently affected, whereas kittens tended to show less severe signs, (3) spread occurred very readily, including via fomites to cats belonging to hospital employees and clients, (4) spread of disease was limited to the affected clinic(s) or shelter, with no spread within the community reported, and (5) the outbreak resolved within approximately 2 months.[10,11]

Figure 111-1 A cat suffering from hemorrhagic feline calicivirus infection (FCV-kaos strain) showing characteristic signs of facial edema and crusting and alopecia of the face and pinnae.



Attempts to make a diagnosis in cases of feline respiratory viral illness are especially encouraged in catteries because knowledge of the causative organism can assist with treatment strategies. Because of the communicability and high mortality associated with virulent FCV infection, microbiologic testing is essential for cats suspected to have the systemic febrile syndrome, and suspect cats should immediately be handled as if they were infected with the organism. Infection with FCV and FHV-1 can be diagnosed using virus isolation or PCR assays from nasal, conjunctival, or oropharyngeal swabs, although oropharyngeal swabs are most likely to yield a diagnosis. For virus isolation, swabs should be transported on ice in a viral transport medium containing antibiotics to prevent bacterial overgrowth; commercial swabs are available for this purpose. The PCR is more reliable for diagnosis of FHV-1 than FCV.[12] However, because asymptomatic cats commonly have positive results using sensitive PCR assays for FHV-1, it may not be possible to prove an association with a particular disease.[13]

The outbreaks of systemic febrile caliciviral disease have demonstrated the importance of control measures to limit the spread of feline respiratory viruses because of the high mortality, poor efficacy of vaccines, and lack of specific treatments. Quick recognition and implementation of effective control measures, including disinfection, quarantine, and testing procedures, are critical to reduce the impact of this disease. These have been described in detail elsewhere.[10]

111.7 FELINE INFECTIOUS PERITONITIS

FIPV infection is caused by feline coronavirus, an enveloped RNA virus. Feline coronaviruses mutate readily, and it is now accepted that the relatively nonpathogenic feline enteric coronavirus (FECV) mutates within the host to form virulent FIPV. Mutation occurs soon after infection with FECV, or years later. Spread of FIP from cat to cat does not occur, so affected cats need not be isolated.

The prevalence of antibodies to feline coronavirus in single cat households is approximately 25%, whereas in multicat households, all cats may have positive titers. In contrast, FIP affects 1 in 5000 cats in single cat households and approximately 5% of cats in catteries. The incidence of FIP is related to levels of virus in the environment, Aimmunosuppression resulting from overcrowding and other stressors, and genetic factors. Purebred cats are more susceptible, and affected cats are usually 3 months to 3 years of age. Occasionally geriatric cats are affected, perhaps because of waning immune function.

Feline coronavirus is highly infectious and is spread via the fecal-to-oral route. FECV replicates in enterocytes and destroys the villus tips, sometimes resulting in mild gastrointestinal signs. Mutation to virulent FIPV is associated with the ability to replicate within macrophages. Cats with a poor CMI response develop pyogranulomatous vasculitis due to deposition of antigen-antibody complexes within the venular epithelium. Pleural and peritoneal effusions develop (effusive FIP). Cats with a partial CMI response are able to slow replication of the virus, with subsequent granuloma formation in a variety of tissues (noneffusive FIP). This may deteriorate to effusive FIP if the CMI response wanes.

Cats with FIP may present with fever, weight loss, anorexia, and lethargy. Other signs and physical examination abnormalities may include dyspnea due to pleural effusion or pneumonia, abdominal distention due to ascites, abdominal masses, icterus, splenomegaly, irregular renomegaly, anterior uveitis, retinal detachments, multifocal neurologic signs, and GI signs relating to organ failure or obstructive intestinal masses.

FIP remains an antemortem diagnostic challenge. The presence of hyperglobulinemia on the complete blood count may increase suspicion for FIP, but it is not present in all cats and may occur with other diseases. The presence of high-protein (5 to 12 g/dl), low-cellularity (predominantly neutrophils) effusion fluid is also supportive of the diagnosis. However, tests such as the serum or effusion albumin-to-globulin ratio, effusion γ-globulin concentration, and the Rivalta test can be associated with false-positive and false-negative results, especially in populations where the prevalence of FIP is low.[14] Serology is not an FIP test. Positive test results only mean exposure to a coronavirus, and many healthy cats have positive titers but never develop FIP. In one study, titers of 1:1600 or greater in cats that were suspected to have FIP had a 94% chance of truly having FIP (compared with 44% for cats with any antibodies).[14] The same study also showed that immunocytochemistry for feline coronavirus on macrophages in effusion fluid had a specificity of 100% for diagnosis of FIP, although the sensitivity was only 57%. The mutation that occurs when FECV becomes virulent FIPV is not predictable, and there is no way to distinguish the viruses based on nucleotide sequence. Because FECV may be found within tissues and body fluids, false-positive results may occur when testing tissues or fluids using RT-PCR. A promising PCR assay has been described that detects viral replication within peripheral blood mononuclear cells.[15] Another study found a connection between viral load in hemolymphatic tissues and development of FIP using a quantitative PCR assay,[16] which may also prove useful for diagnosis. Further studies using these assays are needed in cats with and without FIP. The gold standard for diagnosis of FIP is detection of pyogranulomatous vasculitis on histopathologic examination of biopsy specimens.

Treatment of FIP remains a challenge, and there are few controlled studies of antiviral drug use. Feline recombinant interferon-ω (1 million U/kg SC q72h until remission, then weekly thereafter) and prednisolone (1 mg/kg PO q12h then tapered to q72h) have shown promise in a preliminary study,[17] where 4 of 11 cats with effusive 481 482 disease survived as long as 2 years, although no control cases were included in this study and the diagnosis was not confirmed in the surviving cases. The availability of feline recombinant interferon-ω in the United States is limited.

111.8 SUGGESTED FURTHER READING*

Cornell University College of Veterinary Medicine Animal Health Diagnostic Center web site: *Emerging issues: Canine influenza virus* http://www.diaglab.vet.cornell.edu/issues/civ.asp, 2007, Accessed January 22 *Web site that provides up-to-date information with the number of states with dogs testing positive using serology for canine influenza virus, as well as information on diagnosis and sample submission.*

CE Greene, MJ Appel: Canine distemper. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. ed 3, 2006, Saunders, St Louis, *A book chapter that provides a review of distemper virus infection in dogs, with detailed information on the efficacy and adverse effects of vaccination.*

K Hartmann, C Binder, J Hirschberger, et al.: Comparison of different tests to diagnose feline infectious peritonitis. *J Vet Intern Med*. **17**, 2003, 781, *A large, retrospective case control study involving 488 cats with histopathologically confirmed FIP and 620 controls, reporting the sensitivity, specificity, and positive and negative predictive values of various antemortem diagnostic tests for FIP.*

KF Hurley, JE Sykes: Update on feline calicivirus: new trends. *Vet Clin North Am Small Anim Pract*. **33**, 2003, 759, *A review of FCV infection and the emergence of virulent FCV strains associated with a severe, systemic febrile illness.*

JE Sykes: Feline upper respiratory tract pathogens: herpesvirus 1 and calicivirus. *Comp Cont Educ Pract Vet*. **23**, 2001, 166, *A comprehensive review of the etiology, epidemiology, clinical signs, diagnosis, and treatment of feline viral respiratory disease.*

* See the CD-ROM for a complete list of references

112 Chapter 112 Canine Parvovirus Infection

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112.1 KEY POINTS

- Canine parvovirus (CPV) is a common pathogen in young dogs and usually is seen between the ages of 6 and 20 weeks.
- Parvoviridae are very stable, surviving a pH range of 3 to 9 and temperatures of 60°C for 60 minutes. They can survive for 5 to 7 months in the environment.
- Parvovirus is a highly pathogenic virus that can cause severe vomiting and diarrhea and may be fatal.
- Vaccination against parvovirus is widely practiced, but maternal antibodies can prevent a normal response to vaccination.
- A fecal enzyme-linked immunosorbent assay with high sensitivity and specificity allows for a rapid in-house diagnosis.
- Treatment is mainly supportive with fluid therapy, nutritional support, antiemetics, and antibiotics.
- Reported survival rates for treated dogs with CPV vary widely (64% to 92%), but prompt and aggressive treatment often results in a live animal, the first few days being crucial.

112.2 EVOLUTION OF CANINE PARVOVIRUS 2

Canine parvovirus (CPV)-1 was discovered in 1967 and causes mild diarrhea.[1] A completely new form of CPV that was recognized in 1978 and causes a much more severe disease resembling panleukopenia in cats. A sudden death syndrome due to myocarditis and congestive heart failure was also seen. A parvovirus was isolated in both syndromes and has also been named CPV-2.[2] CPV-2 is genetically distinct from CPV-1 but is closely related to feline and mink parvoviruses, differing by only a few deoxyribonucleic acid (DNA) bases.[3] It is therefore presumed to have evolved from another parvovirus by mutation. It infects feline cells in culture but does not infect cats. It is suspected to have evolved in Europe, with DNA analysis suggesting that this occurred approximately 10 years prior to discovery.[2] It spread around the world rapidly because of the immunologically naïve population of both domesticated and wild members of the family *Canidae*. Subtypes of CPV-2 were recognized in 1979 and 1984 and named CPV-2a and CPV -2b, respectively. CPV-2b is thought to be more pathogenic in some dogs and a study in 1991 showed that it had replaced CPV-2a as the cause of parvovirosis in many regions of the United States.[4] CPV is undergoing continual genetic evolution, and large phenotypic variations can result from single nucleotide substitutions.[5] Recent mutations have been noted and a CPV-2c has been found in Europe and Asia, which appears to cause a relatively mild disease.[6,7]

112.3 SIGNALMENT

CPV is seen most commonly in dogs less than 6 months of age, generally between the ages of 6 and 20 weeks.[8] Infection occurs from either failure of passive transfer, early waning of maternal antibodies, or passive maternal immunity preventing an efficacious response to vaccination. This latter mechanism means that CPV can infect and cause symptoms in vaccinated animals, although this is uncommon.[9] In dogs under 6 months of age there is no gender predilection, but in those over 6 months, male intact dogs are over-represented.[9] Doberman Pinschers, Rottweilers, American Pit Bull Terriers, and German Shepherd Dogs are all thought to be more susceptible than other breeds; however, Rottweilers and Doberman Pinschers have not been shown to have a more severe form of the disease.[9,10] An inherited immunodeficiency in Rottweilers has been postulated as a cause for the increased susceptibility, and von Willebrand disease has been suggested as a potential explanation for the increased likelihood of developing enteritis once infected.[10] A seasonal occurrence has been shown in the United States, with 3 times as many cases seen from July to September than from November to June.[9]

112.4 PATHOGENESIS

CPV is a small, nonenveloped, single-stranded DNA virus that replicates in the nucleus of dividing cells in late the S phase or early G2 phase of the cell cycle. This leads to the preferential infection of rapidly dividing cells, hence the effects of the virus on the bone marrow and the GI tract. CPV is spread by ingestion of virus-containing material from the environment. One gram of feces from an acutely infected dog is thought to contain enough viral material to infect over 10 million susceptible dogs by oral exposure.[8] The virus replicates initially in oropharyngeal lymphoid tissue and is then thought to spread via plasma. Intestinal crypt epithelium is usually infected by day 4 after infection. Antibodies start to appear approximately 5 days after infection and increase to maximal levels by days 7 to 10.[8] Clinical signs appear 4 to 10 days after infection.

When CPV first appeared, myocarditis was common, because passively acquired maternal antibodies were not present. However, these antibodies are now nearly universal and they cover the period of rapid myocardial cell division (completed within the first 2 weeks of life), so myocarditis is now an extremely rare manifestation of CPV infection.

112.5 CLINICAL SIGNS

The leukopenia and enteritis syndrome is by far the most common clinical presentation of CPV infection. Sudden onset of vomiting, depression, abdominal pain, anorexia, and pyrexia are followed 12 to 48 hours later by diarrhea. Antibody titer measurement in unvaccinated dogs suggests that many dogs experience an asymptomatic parvoviral infection or have only mild signs. Diarrhea may not be seen in mild cases, especially in adult dogs.[11] This later appearance or absence of diarrhea should be remembered when considering the differential diagnosis for a vomiting dog. Vomiting can be profuse and can lead to a secondary esophagitis.

The viral destruction of the intestinal crypts leads to intestinal bleeding, and hematochezia is common. The intestinal damage coupled with the neutropenia makes these puppies vulnerable to translocation of bacteria and endotoxin into the bloodstream. Systemic inflammatory response syndrome (SIRS), sepsis, septic shock, and multiple organ dysfunction syndrome may occur in severe cases. Hypoperfusion is usually present to varying degrees and can result in clinical evidence of shock, including tachycardia, poor pulse quality, prolonged capillary refill time, cold extremities, and depression. Mucous membranes are usually pale but may be injected in a dog with concurrent SIRS. When myocarditis does occur, puppies usually die suddenly from pulmonary edema due to congestive heart failure. Retching and dyspnea may precede death. If death does not occur, the focal myocardial necrosis that results can progress to fibrosis or dilated cardiomyopathy.

112.6 DIAGNOSIS

In-house enzyme-linked immunosorbent assay test kits are available that detect fecal antigen via an immunochromatographic assay, allowing for a rapid and inexpensive diagnosis. False-positive results can occur with some fecal viral tests if the dog has received a live parvoviral vaccine during the preceding 5 to 15 days. False-negative results can occur if the sample is taken very early in the disease, so the test should be repeated 36 to 48 hours later if clinical signs are suggestive of parvovirosis. False-negative results can also occur if fecal antigen levels are low or if large numbers of antibodies are present, binding the antigen.[12] Other external laboratory tests are available, including electron microscopy (although CPV-1 is morphologically identical), virus isolation, hemagglutination, and polymerase chain reaction (PCR). PCR is the most sensitive of these and is the test of choice for a dog with suspicious clinical signs that has negative results on in-house testing. A new real-time PCR test has been developed that has improved sensitivity.[6,12] In the past, serology (immunoglobulins G and M) was used to diagnose parvovirosis, but this has, now been surpassed by the aforementioned methods because it is not possible to differentiate between previous subclinical infection, active infection, or the result of vaccination.

A lymphopenia is seen initially as a result of direct lymphocytolysis, followed by a neutropenia due to peripheral consumption and destruction of white blood cell precursors in the bone marrow. This leukopenia can aid in diagnosis but has been reported in less than 50% of infected dogs.[9] Biochemical changes may include hypoproteinemia, hyperbilirubinemia, elevated liver enzymes, hypokalemia, hypoglycemia, and a prerenal azotemia.[13] Thrombocytopenia, prolonged activated clotting time, prothrombin time, activated partial thromboplastin time, and increased D-dimer levels can be seen in severe cases suggesting disseminated intravascular coagulation (DIC). Hypercoagulability has also been noted in dogs suffering from CPV enteritis without DIC.[14] This has been postulated to be due to hyperfibrinogenemia and a reduction in antithrombin activity.[14]

Diagnostic imaging can be useful to rule out other causes of vomiting and diarrhea such as intestinal obstruction; however, radiography often reveals a dilated small bowel ileus that is sometimes difficult to differentiate from surgical ileus. Intussusception is both an important differential diagnosis for parvovirus and also a potential sequela. Thoracic radiographs may be required if aspiration pneumonia is suspected.

112.7 TREATMENT

Symptomatic supportive treatment with fluids, antibiotics, and antiemetics forms the mainstay of therapy for CPV.

112.7.1 Fluid Therapy

Even if infection is not clinically apparent, the vast majority of animals with symptomatic parvovirus infection will be dehydrated. Relying on skin tenting is insensitive in puppies because they have very mobile skin (see Chapter 174, Critically Ill Pediatric Patients). Also, puppies grow very quickly and even if a recent weight was obtained, the full extent of fluid loss may be underestimated if the animal has required prolonged hospitalization. Except for the mildest of cases, intravenous fluid therapy is necessary. 483 484

Intravenous fluid therapy should always address hypoperfusion first and then dehydration. An isotonic, balanced electrolyte solution should be chosen such as Normosol-R, Plasmalyte 148, 0.9% sodium chloride, or lactated Ringer's solution (see Chapters 64 and 65, Daily Intravenous Fluid Therapy and Shock Fluids and Fluid Challenge, respectively). Aggressive fluid rates may be necessary initially and the response to therapy closely assessed. In patients with septic shock, hypoalbuminemia, or vasculitis, response to isotonic crystalloid fluid therapy can be inadequate and colloid therapy may be necessary. The larger molecules present in hetastarch may be preferable because vasculitis could result in extravasation of albumin. Plasma may be beneficial because it contains clotting factors (useful for the treatment of prolonged enteral bleeding or to aid in cases of DIC) and albumin. Whole blood may be necessary if the puppy is severely anemic. Plasma lactate quantitation can aid in guiding fluid resuscitation, although very young puppies normally have higher lactate values (see Chapter 174, Criticaly Ill Pediatric Patients). Once hypoperfusion is controlled, dehydration is corrected over 24 to 48 hours, and fluid rates should be titrated each day to account for ongoing losses. Frequent monitoring is necessary to assess the fluid therapy plan.

If the animal is anorexic or if hypokalemia is present, potassium chloride should be added to the fluids but only after hypoperfusion has been corrected (see Chapter 55, Potassium Disorders). GI losses can also result in hyponatremia and hypochloremia. Blood glucose levels are often low as a result of immature enzyme systems, sepsis, inadequate glycogen stores, and decreased caloric intake. Dextrose supplementation may be required, potentially exacerbating a concurrent hypokalemia.

Maintaining catheter sterility can be very difficult in puppies with CPV when they are vomiting and producing copious volumes of diarrhea. Careful bandaging and regular checking of catheter sites are required. Although a more durable jugular catheter may appear desirable, the hypercoagulability seen in CPV-infected puppies can lead to jugular thrombosis. In mildly affected animals, treatment at home with subcutaneous fluid administration can be attempted, but this is suboptimal in more seriously affected animals because it will not effectively restore circulating volume in a timely manner.

112.7.2 Antibiotics

Dogs with evidence of sepsis or that are pyrexic or severely neutropenic definitely require antibiotic therapy. However, any dog with blood in its feces is at risk of bacterial translocation, so broad-spectrum, bactericidal antibiotics should be considered in most patients. Afebrile, neutropenic dogs can be treated with an antibiotic such as potentiated amoxicillin, but if evidence of sepsis is present, antibiotics with good activity against gram-positive, gram-negative, and anaerobic organisms are recommended. Parenteral administration is preferred because vomiting and delayed gastric emptying may result in poor reliability of absorption of oral preparations. Ampicillin and amikacin can be used, but care must be taken to ensure renal perfusion is optimized prior to therapy with the latter drug. Urine sediment should be monitored daily for proteinuria, glucosuria, or casts. Enrofloxacin can also be used in combination with ampicillin, but adverse effects on cartilage of growing animals have been shown histologically, so it is usually avoided in puppies. Ideally, antibiotic choice is guided by blood culture, but this rarely is performed. Subsequent infection by multidrug-resistant bacteria may occur in some cases.

112.7.3 Antiemetics

Vomiting leads to dehydration, electrolyte and acid-base disturbances, and esophagitis. Nausea causes increased morbidity and anorexia. Metoclopramide, chlorpromazine (used with care in hypovolemic animals because of its vasodilatory effects), and ondansetron or dolasetron can all be effective (see Chapter 182, Antiemetics).

Although the latter two are expensive, they are useful when vomiting is unresponsive to other drugs. A recent retrospective study found that the use of antiemetics in dogs with CPV was associated significantly with longer hospitalizations; however, whether this was merely due to differing drug regimens in more severely affected animals was not clear.[15]

112.7.4 Nutrition

Once vomiting has been controlled, the puppy should be encouraged to eat small, frequent meals of a low-fat, easily digestible diet (see Chapter 13, Enteral Nutrition). It is not necessary to withhold feedings in animals with diarrhea. A nasoesophageal tube can be placed if the patient is anorexic. One study suggested that even if an animal is still vomiting, nasoesophageal feeding is well tolerated and results in earlier clinical improvement.[16] Great care must be taken to monitor these patients for aspiration of ingesta, especially because they often are located in an isolation ward and lack frequent patient observation. Nasogastric tubes can be used to allow gastric decompression, which may decrease nausea and lessen the risk of aspiration pneumonia in animals with refractory vomiting. In smaller puppies the bore of the nasogastric tube may be so narrow that decompression is not possible. Electrolytes and acid-base status must be monitored closely to allow early detection and management of hypochloremia, hypokalemia, or metabolic alkalosis. Enteral nutrition is preferred because it helps maintain intestinal mucosal integrity and decreases bacterial translocation. Total or partial parenteral nutrition can be administered when needed, but meticulous catheter asepsis and monitoring should be performed because these animals are commonly immunosuppressed and coagulopathic.

112.7.5 Antiviral Drugs

Feline interferon (type omega) is now licensed for treatment of parvovirus in dogs in Europe, Japan, Australia, and New Zealand. In one study of 94 clinical cases it was found to decrease mortality rates by 4.4-fold and also to decrease clinical signs compared with dogs not given the drug.[17] The most successful dosing regimen appears to be 2.5 mU/kg IV q24h for 3 consecutive days. It is not licensed in the United States and further research would be beneficial.

There has been interest in oseltamivir in dogs with CPV, but no clinical trials have been performed.

112.7.6 Gastric Protectants

Histamine-2 receptor antagonists such as ranitidine, cimetidine, and famotidine can be used in animals with esophagitis or gastritis; however, the efficacy of ranitidine in significantly altering gastric pH has been questioned.[18] Sucralfate can also be administered if vomiting is controlled adequately. If upper GI tract ulceration is suspected (e.g., if melena or vomiting of “coffee grounds” is seen), omeprazole (or injectable esomeprazole) may be more effective than other agents at promoting healing (see Chapter 181, Gastrointestinal Protectants).[18]

112.7.7 Controversial Treatments

Antiendotoxin has been suggested for the treatment of parvovirosis. It is used diluted 1:1 with crystalloid fluids, administered over 30 to 60 minutes, and should be given before antibiotics that can cause endotoxin release from bacterial cell walls. Because the endotoxin is of equine origin, it can cause anaphylaxis and should not be used for repeated dosing more than 7 days apart. Conflicting results have been published, with one study suggesting increased mortality rates associated with antiendotoxin, but another found that survival rates increased with its use.[19,20] Serum from recovered dogs has also been used (1.1 to 2.2 ml/kg IV) to provide antibodies, but this information is anecdotal and no controlled clinical trials have been reported. Granulocyte colony–stimulating factor may increase the white blood cell count in severely leukopenic patients, but it is expensive and has not been shown to improve CPV survival rates.[21,22]

112.8 VACCINATION

Most adult dogs are immune to CPV, either via juvenile infection, subclinical adult infection, or immunization.[11] Susceptible animals are therefore mainly puppies. Pups with seronegative nursing dams or pups that do not get any colostrum are obviously susceptible to infection. If the dam has low antibody titers, pups may acquire protection for only 4 to 6 weeks after birth. Dams with high antibody titers may pass on protection from parvovirus that lasts for 12 to 20 weeks.[23]

Earlier vaccines were sometimes ineffective because preexisting maternal antibodies neutralized vaccinal antigens. This led to protocols of vaccination every 2 to 3 weeks beginning at 6 to 8 weeks of age until 18 to 20 weeks of age. Vaccines were then developed in the mid-1990s that had higher antigen levels and were also more effective immunostimulants, obviating the need for such frequent administration.[24,25] Some newer vaccines may provide protective titers for up to 3 years.[26]

The antibody response to vaccination and the requirement for boosters can be assessed by hemagglutination inhibition. The commonly used so-called *protective titer* of at least 1:80 is incompletely protective in some cases, although signs were less severe in affected animals.[27] Despite vaccination, dogs can still suffer from parvovirus infection: 12% of dogs with CPV brought to a referral hospital were vaccinated, compared with 64% of dogs with nonenteric illness during the same period.[9] Live vaccines generally are used, but killed virus vaccines are available and advised for use in unvaccinated pregnant bitches.

112.9 PREVENTION OF TRANSMISSION

CPV-infected dogs should be isolated and barrier nursed to avoid the risk of transmission to other patients in the hospital. They shed virus into the surrounding environment, so thorough cleaning is required with agents that kill parvovirus, such as bleach (dilute 1 part bleach to 32 parts water) or alkyl dimethyl benzyl ammonium chloride. Soft furnishings can be difficult to clean effectively, so if the environment cannot be effectively sterilized, such as in a home, breeding should be discontinued and no unvaccinated, naive animals should be introduced for 1 year. An animal that has recovered should be kept away from other dogs initially, because they have been shown to shed virus for up to 39 days post infection. Careful disposal of feces is required.[27]

112.10 SUGGESTED FURTHER READING*

LT Glickman, LM Domanski, GJ Patronek, et al.: Breed-related risk factors for canine parvovirus enteritis. *J Am Vet Med Assoc*. **187**, 1985, 589, *A retrospective study of 96 dogs with CPV revealing that Doberman Pinschers and Rottweilers were overrepresented; survival rate 64%.*

TC Gore, N Lakshmanan, KL Duncan, et al.: Three-year duration of immunity in dogs following vaccination against canine adenovirus type-1, canine parvovirus, and canine distemper virus. *Vet Ther*. **6**, 2005, 5, *A challenge-of-immunity study showing that immunity was present in 23 of 23 dogs (100%) 3 years after their* *second vaccination with a multivalent, modified live vaccine containing canine adenovirus type 2, CPV, and canine distemper virus*.

DM Houston, CS Ribble, LL Head: Risk factors associated with parvovirus enteritis in dogs: 283 cases (1982-1991). *J Am Vet Med Assoc*. **208**, 1996, 542, *A retrospective analysis of 283 cases of CPV examining risk factors for disease*.

RV Pollock, MJ Coyne: Canine parvovirus. *Vet Clin North Am Small Anim Pract*. **23**, 1993, 555, *An older review of CPV*.

J Prittie: Canine parvoviral enteritis: a review of diagnosis, management and prevention. *J Vet Emerg Crit Care*. **14**, 2004, 167, *A thorough review of diagnosis, treatment, and prevention of canine parvoviral infection*.

* See the CD-ROM for a complete list of references

113 Chapter 113 Endocarditis

Merilee F. Costello, DVM, DACVECC

113.1 KEY POINTS

- Infective endocarditis (IE) is an uncommon clinical disease associated with a high mortality.
- Diagnosis is challenging because the signs are nonspecific and a variety of organ systems can be affected.
- Using criteria extrapolated from human medicine may improve our diagnostic capabilities.
- The vegetative lesions associated with IE make eradication of the infectious organism difficult.
- Antimicrobial therapy should consist of long-term bactericidal administration.
- The prognosis for patients with IE is poor.
- Antimicrobial prophylaxis should be considered in high-risk patients that are undergoing surgical or dental procedures.

113.2 INTRODUCTION

Endocarditis is defined as inflammation of the endocardial surface of the myocardium. In veterinary patients, the most commonly recognized cause is infective endocarditis (IE). This occurs when an infectious agent, generally a bacterium, invades the endocardial surface of the myocardium. This infection most often affects the valves and may lead to myocardial dysfunction and cardiovascular compromise. It is important to remember, however, that the clinical signs of IE are not limited to the effects on the heart itself. Systemic signs occurring secondary to the infection often predominate. Endocarditis has been called the great imitator because of the variable and indistinct clinical signs in these patients, making definitive diagnosis challenging. Knowledge of the pathophysiology, etiology, risk factors, and clinical signs may heighten suspicion of this disease. Definitive diagnosis can be difficult, and aggressive, long-term therapy is required. Prognosis for this condition remains guarded, but increased awareness and preventive measures may limit the mortality associated with endocarditis in veterinary patients.

113.3 PATHOPHYSIOLOGY

An understanding of the pathophysiology of endocarditis is essential for recognition, diagnosis, and appropriate treatment. In patients with bacterial endocarditis, bacteremia must be present, either permanent or transient. However, it is important to note that although transient bacteremia is common, IE is an uncommon sequela.[1] In a normal animal, these bacteria are removed rapidly by cells of the mononuclear phagocytic system. In IE, the infectious organism in the bloodstream attaches to the endothelium, most commonly affecting the heart valves. The high turbulence associated with opening and closing of the valves predisposes this area to endothelial disruption and bacterial colonization. The aortic and mitral valves are affected most commonly, likely a result of the high forces that are applied to them.[1-12,15] In an area of the heart that has undergone damage, the bacteria adhere to a previously formed lesion within the endocardium. Once the bacteria adhere to the endocardium, a vegetative lesion is formed. These vegetative lesions consist of a combination of fibrin, platelets, red blood cells, and bacteria.[2] The bacteria are often very concentrated and buried deep within the lesion, protecting them from the host's immune system as well as exogenously administered antimicrobial therapy.[7]

It has been suggested that the development of endocarditis depends of the presence of one or more of the following factors: bacteremia, previous damage to the endocardium, the formation of a sterile thrombus at the site of endocardial damage, and a high titer of antibodies against the infectious agent, which causes clumping of the organisms.[8] Unfortunately, in veterinary patients, many of these factors are not easily identified antemortem.

113.4 ETIOLOGY

In most cases, IE is secondary to a bacterial infection. The most commonly reported bacteria associated with IE include *Streptococcus* spp, *Staphylococcus* spp, and *Escherichia coli*. [1,2] Other bacteria reported as a cause of endocarditis in dogs include *Corynebacterium* spp, *Pseudomonas* spp, *Pasteurella* spp, *Erysipelothrix rhusiopathiae,* and *Actinomyces turicensis*. [3,9,17] Rickettsial organisms have been implicated, and fungal infection as a cause of endocarditis is rare in dogs.

Culture-negative endocarditis secondary to *Bartonella* species has been reported in dogs.[6,10,11] There is a high prevalence for *Bartonella henselae* bacteremia in the feline species, even in normal cats. There are, however, reported cases of endocarditis in cats suspected to be due to *Bartonella* infection.[5] *Bartonella vinsonii* subspecies *berkhoffii* is the only type of *Bartonella* to be isolated in the dog. *Bartonella* spp are fastidious, gram-negative bacilli that reside within or on the surface of red blood cells, and special techniques are required to isolate them in blood cultures. In cases of systemic infection secondary to *Bartonella,* serum immunofluorescent antibody titers are significantly increased in most patients.[7,10,11] In general, an indirect fluorescent antibody assay immunoglobulin G (IgG) titer greater than 64 indicates previous or current exposure to the organism.[11]

113.5 RISK FACTORS

Any condition that results in either transient or permanent bacteremia can predispose an animal to IE. Underlying 486 conditions implicated in causing endocarditis include prostatitis, 487 discospondylitis, pyoderma, pyelonephritis, perianal fistulas, infected wounds or abscesses, cellulitis, and severe dental disease.[1,2,5,6,12] Dogs undergoing dental prophylaxis develop a transient bacteremia.[13] In humans, oral pathogens have been implicated in IE as well as atherosclerosis and coronary artery disease.[14] In our veterinary patients, a direct causal relationship between dental disease and endocarditis has never been documented. However, one report of mitral valve endocarditis in a dog after dental cleaning suggests that acquired IE may occur after dental prophylaxis in our patients.[15]

Another factor in the occurrence of IE is host susceptibility. Any disease that weakens the immune system or impairs host defenses may predispose an animal to bacteremia and IE. Neoplasia, diabetes mellitus, immunosuppressive medications, and glucocorticoids may increase the risk of IE. Although hyperadrenocorticism has significant effects on a host's immune response, the incidence of IE in dogs with hyperadrenocorticism is very low.[12] Glucocorticoid administration in cases of IE is very common, likely a result of vague signs or presumed immune-mediated disease. In dogs with mitral valve endocarditis, the survival rates in those that received glucocorticoids were significantly lower than in dogs that did not receive them.[2]

Congenital cardiac abnormalities are a significant risk factor in both humans and dogs. Subaortic stenosis is an important risk factor in dogs, and a retrospective analysis of 96 dogs with subaortic stenosis documented the occurrence of IE in 6.3% of those with mild to moderate stenosis.[16] In patients with subaortic stenosis, the high-velocity blood flow damages the surface of the aortic valve, predisposing it to bacterial colonization. Interestingly, although mitral valve disease can also lead to valvular damage, no relationship between endocardiosis and IE has been established.

Other, less common, risk factors include previous IE, cardiac surgery, and pacemaker implantation.[7] Hypercoagulability may be associated with numerous underlying diseases, such as protein-losing nephropathy, hyperadrenocorticism, diabetes mellitus, pancreatitis neoplasia, or immune-mediated disease. This increased ability to form clots may predispose dogs to IE, although this has never been clinically proven in veterinary patients.

113.6 CLINICAL PRESENTATION

Dogs affected by IE are generally medium-sized to large breed dogs with an average age of 4 to 8 years.[2] Dogs younger than 2 years or older than 10 years are rarely affected. There appears to be breed predisposition, with Newfoundlands, German Shepherds, Golden Retrievers, Labrador Retrievers, Boxers, Doberman Pinschers, and Rottweilers more commonly affected.[2,7,12,16] Male dogs are affected more frequently than female dogs, at a ratio of 2:1.[2] There are no reports of the prevalence of IE in cats, although it appears to be rare.[5,6]

The clinical signs associated with endocarditis in dogs are often vague and generally related to the widespread systemic effects. Common initial complaints include lethargy, depression, shivering, weight loss, anorexia, weakness, vomiting, diarrhea, lameness, tachypnea, and dyspnea.[1-10,12,17] Less commonly reported are syncope, epistaxis, paraparesis, polydipsia, hematuria, hyphema, retinal hemorrhage, and petechiae.[3,7] Physical abnormalities in dogs are also variable and commonly consist of fever, lameness, heart murmur (systolic or diastolic), tachycardia, and arrhythmias. Fever is very common in dogs with IE, occurring in 50% to 70% of patients. Other clinical signs related to embolic consequences in IE may also be identified, such as neurologic abnormalities, abdominal pain, or pulse deficits.

There are very few data on the clinical presentation of IE in cats.[5,6] In a report of vegetative endocarditis in six cats, the patients consisted of neutered young to middle-aged cats, and males were not overrepresented. Complaints included coughing, anorexia, dyspnea, and hemoptysis. It is important to note that none of the cats in this study had a fever, and one cat was borderline hypothermic. Four of the cats arrived at the hospital in congestive heart failure, and one cat had pericardial effusion.[5] It is important to remember, however, that this was a very small study and therefore generalizations cannot be made about the clinical features of IE in cats based on these data. Further studies are needed in this patient population to better clarify the incidence, predisposing factors, and clinical picture.

As with clinical signs, the laboratory changes are extremely variable. Factors such as the underlying source of the bacteremia, the degree of cardiac compromise, the presence of congestive heart failure, and the severity of organ damage all affect the clinicopathologic changes in a given animal. Approximately 50% to 60% of dogs with endocarditis have a normocytic, normochromic, nonregenerative anemia.[2,3,5,6] These patients often have a leukocytosis, frequently characterized by neutrophilia and/or monocytosis. In severe cases, degenerative leukocytosis may be present.[1-3,7] In a case report of IE in a cat, there was a regenerative left shift, but in the aforementioned study of cats with endocarditis, only two of the six subjects had a leukogram demonstrating inflammation.[5,6]

Serum chemistry changes will also differ based on the systemic consequences of the endocarditis. Renal failure or protein-losing nephropathy can occur in animals with renal infarction or severe glomerulonephritis. Other reported abnormalities in dogs include increased serum alkaline phosphatase levels, hypoalbuminemia, and hypoglycemia. In a study of cardiovascular infections in dogs, abnormalities in alkaline phosphatase, albumin, or glucose concentration occurred in 67%. In addition, dogs with abnormalities of two or three of those diagnostic tests had a worse prognosis when compared with dogs with normal levels.[1] In cats, reported abnormalities include hyperglycemia, hypocalcemia, hypoalbuminemia, hyperglobulinemia, and hematuria.[6]

Although an integral physical examination finding, a cardiac murmur is heard in only 50% to 75% of dogs with endocarditis. The infection in these patients can lead to significant valvular damage, including perforation, tears, deformities, irregularities, and rupture of the valve leaflets or chordae tendinea. The severity and character of the heart murmur will vary depending on the valve affected and on the degree of valve damage. The most common heart murmur associated with endocarditis is a systolic murmur, but a diastolic murmur may be noted in dogs with endocarditis of the aortic valve.[2] In cats, only systolic murmurs have been reported.[5,6] Conduction disturbances and arrhythmias are common in dogs with endocarditis. Reported arrhythmias include supraventricular and ventricular tachycardia, premature ventricular beats, atrioventricular block, atrial fibrillation, left bundle branch block, and complete heart block.[2,7,8]

Although not a sensitive test for the diagnosis of endocarditis, thoracic radiographs are important in patients with suspected endocarditis, mainly to evaluate for the existence of volume overload or congestive heart failure and pulmonary edema. The latter plays an important role in the treatment of these patients and is a negative prognostic indicator.[2,3,7]

Septic embolization is one of the most devastating sequelae of endocarditis. Embolization can occur in the kidneys, spleen, coronary circulation, brain, intestines, or peripheral vascular beds. Emboli can impair blood flow to vital organs and spread infection to other sites in the body. Associated clinical signs will differ depending on the vascular bed(s) affected.

The bacteremia associated with endocarditis results in stimulation of both humoral and cell-mediated immunity. This results in elevations in circulating immunoglobulins, including IgG, IgM, and IgA. These circulating immunoglobulins can lead to disseminated immune complexes, which can deposit in the joints or the kidneys and result in immune-mediated polyarthropathy or glomerulonephritis. These patients often exhibit lameness, and both infective and noninfective synovitis have been identified in dogs with bacterial endocarditis.[17]

113.7 DIAGNOSIS

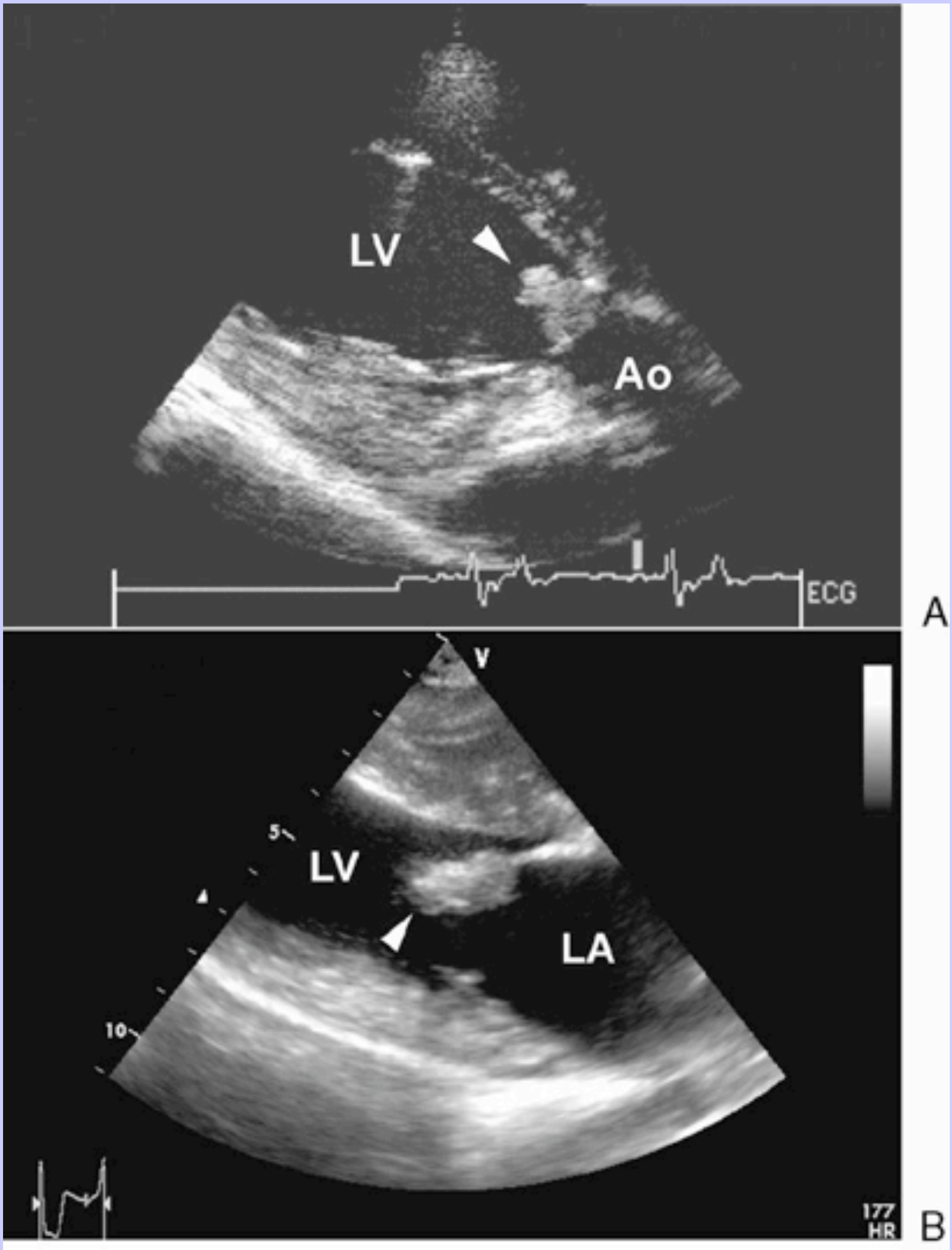
Antemortem diagnosis of endocarditis is difficult and requires integrating the clinical presentation with additional diagnostic measures. As previously discussed, the changes seen on routine blood work and radiographs are often vague and nonspecific. For definitive diagnosis of endocarditis, blood cultures and echocardiography are required.

Blood cultures and sensitivity testing are an integral part of the diagnostic testing in patients suspected to have endocarditis. Blood cultures are important not only for diagnosis but also for choosing the appropriate antimicrobial therapy. Ideally blood cultures should be obtained before initiating antibiotic therapy, but intervention should not be delayed while awaiting blood culture results.

When obtaining blood samples for culture, aseptic technique should be used to minimize contamination. The samples should be drawn from either a new, aseptically placed jugular catheter, or from an aseptically prepared peripheral vein.[18] At least two samples should be taken 10 minutes apart. Ideally, different venipuncture sites should be used, and each site must be clipped, scrubbed, and sterile gloves worn when obtaining the sample. In dogs, 7 to 10 ml of blood should be obtained for each sample and the blood split between aerobic and anaerobic culture media. The access point on the culture bottle should be cleaned with 70% alcohol and allowed to dry. Pediatric culture vials, which require only 1 to 3 ml of blood, can be used in cats and small dogs to minimize the volume that is required. Other culture techniques such as lysis centrifugation or gene amplification by polymerase chain reaction may also be helpful for diagnosis.[7] Because *Bartonella* spp are difficult to culture serum immunofluorescent antibody titers should also be considered whenever there is high suspicion of endocarditis.

Echocardiography is an essential tool in the diagnosis of endocarditis. It is important to remember, however, that echocardiography is not 100% sensitive or specific. Many variables affect the sensitivity and specificity of echocardiographic evaluation for endocarditis, including the affected valve, the quality of the image, and the expertise and experience of the sonographer. In human medicine it has been suggested that transesophageal echocardiography replace transthoracic echocardiography to improve sensitivity. In a study of human patients with endocarditis, transesophageal studies detected lesions in 90% of patients, as compared with 60% to 70% when transthoracic evaluation was used.[19,20] Unfortunately, transesophageal echocardiography in veterinary medicine is limited to patients that are heavily sedated or under anesthesia. In those with endocarditis, an echogenic, intracardiac mass may be seen on the aortic or mitral valve (Figure 113-1). Classically these lesions are located on the cranial (anterior) leaflet, but not in all cases.[11] Lesions on the aortic valve often are easier to recognize because the changes seen with myxomatous degeneration may obscure the diagnosis in cases of mitral valve endocarditis. Other changes that may be seen with aortic endocarditis include chamber enlargement and impaired contractility secondary to high-pressure volume overload.

Figure 113-1 Two-dimensional echocardiogram showing vegetative lesion on the aortic valve (**A;** *arrow*) and mitral valve (**B;** *arrow*) of a dog. (Courtesy Dr. Mark Oyama.)



In human medicine, specific criteria have been developed in an attempt to improve the diagnosis of endocarditis.[20] These criteria, known as the *Duke diagnostic criteria,* use a combination of physical examination abnormalities, echocardiographic changes, and blood culture results (Box 113-1). Using these criteria in our veterinary patients may improve diagnostic ability for patients with this disease.

113.8 TREATMENT

Treatment of patients with IE consists of eradication of the infectious agent and treatment of the systemic 488
complications. Because of the nature and composition of the vegetative lesion, the infection is not easily cleared. 489
The complex matrix within these lesions makes antimicrobial penetration difficult, and relapse is common.

113.8.1 Box 113-1 Duke Diagnostic Criteria

113.8.1.1 Criteria

Definitive clinical diagnosis is made if the patient meets two major criteria, or one major and three minor criteria, or five minor criteria.[19]

113.8.1.1.1 Major Criteria

- Positive blood culture results
  - Organism typical for IE on blood cultures from two sites
  - Persistently positive blood culture results
- Evidence of endocardial involvement
  - Oscillating intracardiac mass on valve or supporting structures
  - Abscess
  - New valvular regurgitation

113.8.1.1.2 Minor Criteria

- Predisposing heart condition
- Fever

Vascular phenomena

Major arterial emboli, septic pulmonary infarct, intracranial hemorrhage

Immunologic phenomena

Glomerulonephritis, polyarthritis

Microbiologic evidence

Positive blood culture in only one sample

Serologic evidence of active infection by an organism consistent with IE

Echocardiogram

Consistent with IE but not meeting previous criteria

IE, Infectious endocarditis.

To prevent recurrence, long-term bactericidal therapy is essential. In human medicine, the American Heart Association recommends parenteral therapy for at least 4 to 6 weeks. Unfortunately, this is not generally feasible in veterinary patients. In severely debilitated animals, hospitalization often is required for treatment of the systemic effects of the infection, and intravenous antibiotics play an integral role. It has been suggested in that affected animals receive at least 1 to 2 weeks of intravenous therapy, followed by subcutaneous administration for several weeks before beginning a regimen of 1 to 2 months of oral administration.[12] While waiting for culture and sensitivity results, or in patients with a negative blood culture findings, empiric broad-spectrum antibiotic therapy should be administered. Recommended antibiotic combinations include clindamycin plus enrofloxacin, or a combination of penicillins and aminoglycosides.[7,12] Aminoglycoside therapy must not be used in any patient with renal compromise, and therapy should be limited to 5 to 7 days, with concurrent fluid therapy to minimize renal toxicity and frequent urine sediment monitoring. As single-drug therapy, the third-generation cephalosporins may be beneficial.[7] In all patients, blood cultures should be repeated 4 weeks after treatment begins to determine whether or not the organism has been eradicated. In veterinary patients with *Bartonella* endocarditis, the ideal antimicrobial agent is not known. In humans, ciprofloxacin, gentamicin, ceftriaxone, doxycycline, erythromycin, and azithromycin have all been effective.[7]

Glucocorticoid therapy is often considered in these patients because of the vague nature of the clinical signs and concerns for the development of immune-mediated disease. However, glucocorticoid use has been associated with increased mortality in dogs with IE and should be avoided if possible.[2]

In human medicine, anticoagulant therapy in patients with IE is controversial. Anticoagulant therapy has been associated with more severe neurologic damage and a worse outcome.[21] In experimental studies in rabbits, low-dose (antiplatelet) aspirin has been associated with a reduction in the vegetative density, bacterial titer within the vegetation, bacterial dissemination, and embolic events.[22,23] Although these initial experimental studies were promising, a randomized, double-blinded, placebo-controlled trial of aspirin treatment in human patients with IE did not improve vegetation resolution or reduce the risk of embolic events.[24] Additionally, there was no reduction in the occurrence of cerebral lesions, and aspirin may increase the risk of bleeding. Based on the results of this study, the authors concluded that aspirin is not indicated in the early treatment of patients with IE. In veterinary patients, further clinical studies are needed before definitive recommendations can be made.

There are generally widespread systemic effects associated with IE. Congestive heart failure, acute renal failure, neurologic damage, and disseminated intravascular coagulation are potential sequelae. Careful monitoring and aggressive supportive care are necessary to improve outcome in these patients.

113.9 PROGNOSIS

The prognosis for IE varies depending on a number of factors. The location of the lesion, the severity of the systemic complications, the virulence, and the antibiotic susceptibility or resistance of the infectious agent can play a vital role in the outcome of patients. The overall prognosis is poor, and the reported mortality is 60% to 95% in dogs, and 67% in cats.[1-3,5] In dogs, favorable criteria for survival include involvement of only the mitral valve, lack of systemic embolization, and negative blood culture results for 3 months after therapy. Rapid diagnosis and appropriate treatment significantly improve outcome.[2,3]

113.10 PREVENTION

Prophylactic antibiotic therapy is controversial, primarily because of concerns over antibiotic resistance and questionable efficacy. However, because of the high mortality associated with IE, prophylactic antibiotics should be considered in any high-risk patient undergoing invasive or traumatic surgery. The following protocols have been recommended: ampicillin sodium 30 mg/kg IV, or clindamycin phosphate 10 mg/kg IV. These antibiotics should be administered 1 hour before and 6 hours after the procedure.[7]

113.11 CONCLUSIONS

IE is a rare but serious disease in dogs and cats. The clinical signs are often vague and nonspecific, making diagnosis challenging. Systemic sequelae can be severe and affect multiple organ systems. Rapid diagnosis and treatment are essential to minimize mortality, but the overall prognosis for these cases is poor.

113.12 SUGGESTED FURTHER READING*

TC de Francesco: CVT update: Infectious endocarditis. In JD Bonagura (Ed.): *Kirk's current veterinary therapy XIII: small animal practice*. ed 13, 2000, Saunders, Philadelphia, *An excellent review of advances in the diagnosis, treatment, and prevention of IE. Also includes information on culture-negative IE.*

RD Kienle, WP Thomas, PD Pion: The natural clinical history of canine congenital subaortic stenosis. *J Vet Intern Med*. **8**, 1994, 423, *A retrospective analysis of 96 dogs with subaortic stenosis. Documents the demographics, breed predilections, clinical course, and association with endocarditis*.

R Malik, VR Barrs, DB Church, et al.: Vegetative endocarditis in six cats. *J Fel Med Surg*. **1**, 1999, 171, *The only study characterizing vegetative endocarditis in a feline population. Discusses unique features of this disease in feline patients. Clinical signs, diagnostic testing, bacterial isolates, and outcome reported.*

* See the CD-ROM for a complete list of references

114 Chapter 114 Urosepsis

Lillian R Aronson, VMD DACVS

114.1 KEY POINTS

- Urosepsis is uncommonly diagnosed in the veterinary patient.
- *Escherichia coli* is the most frequently diagnosed uropathogen in animals with urosepsis.
- In most animals with urosepsis, bacteria isolated from the rectal, genital, and perineal areas serve as the principal source of infection.
- Patients with a urinary tract infection (UTI) and risk factors such as an anatomic abnormality, a urinary tract obstruction, nephrolithiasis, prior urinary tract disease, renal failure, neurologic disease, diabetes, hyperadrenocorticism, and immunosuppression are more prone to urosepsis.
- Causes of urosepsis that have been identified in the veterinary patient include pyelonephritis, bladder rupture, prostatic infection, testicular and vaginal abscess formation, pyometra, and catheter-associated UTIs.
- Treatment should be instituted as soon as possible and often includes a combination of intravenous fluid therapy and broad-spectrum antibiotics, correction of the underlying condition, and attempts to correct any predisposing or complicating factors.

114.2 INTRODUCTION

Urosepsis, uncommonly reported in veterinary medicine, refers to sepsis associated with a complicated urinary tract infection (UTI). In humans, the source of the infection can be the kidney, bladder, prostate, or genital tract.[1] More specifically, urosepsis in humans has been associated with acute bacterial pyelonephritis, emphysematous pyelonephritis, pyonephrosis, renal abscess formation, fungal infections, bladder perforation, and prostatic and testicular infections.[2-5] Additionally in human patients, urinary catheter-associated infections have also resulted in sepsis.[6-8] Although many of these conditions are often diagnosed in the veterinary patient, little information exists in the veterinary literature regarding the incidence of urosepsis as a complication of these conditions. In one retrospective study looking at sepsis in small animal surgical patients, the urogenital tract was identified as the source of infection in approximately 50% of the cases.[9] Of 61 dogs included in the study, sources of urosepsis included pyometra (14), prostatic abscess formation or suppuration (12), testicular abscess formation (3), renal abscess formation (3), and vaginal abscess formation (1). Of four cats included in the study, one had a pyometra and a second cat had a ruptured uterus. This chapter will discuss the pathogenesis of urosepsis, as well as review the veterinary literature to determine what conditions in veterinary medicine have been associated with this disease. Accurate recognition of these complicated UTIs and appropriate, timely treatment are necessary to prevent morbidity and mortality.

114.3 PATHOGENESIS

Urosepsis is a clinical condition that occurs secondary to a systemic bacterial infection originating in the urogenital tract and the associated inflammatory response. In most cases of urosepsis, bacteria isolated from the rectal, genital, and perineal areas serve as the principal source of infection.[10] These bacteria can then migrate from the genital tract to the lower and then upper urinary tracts.[10] As in human patients, *E. coli* is the most common uropathogen affecting dogs and cats and accounts for up to one half of the urine isolates.[10-16] Gram-positive cocci, including *Staphylococci, Streptococci*, and *Enterococci,* account for up to one third of bacteria isolated and, although uncommonly diagnosed, *Pseudomonas, Klebsiella, Pasteurella, Corynebacterium,* and *Mycoplasma* account for the remaining isolates.[12,17-19] In humans, gram-negative sepsis is frequently caused by infections originating in the urinary tract.[6,13]

Because *Escherichia coli* is the most common pathogen affecting the urinary tract of both human and veterinary patients, and consequently the most common pathogen leading to urosepsis, its virulence has been investigated extensively. Although several hundred serotypes of *E. coli* are known, fewer than 20 account for most bacterial UTIs.[20] In dogs and humans, most of the strains that cause symptomatic UTIs belong to a small number of serogroups (O, K, and H) (see Chapter 109, Gram-Negative Infections).[13] Certain properties that may enhance bacterial virulence include the presence of a particular pilus that mediates attachment to uroepithelium, hemolysin, aerobactin, resistance to the bactericidal action of serum, and rapid replication time in urine.[10-13] In patients with structural or functional abnormalities of the urinary tract or those with altered defenses, infections can be caused by gram-negative aerobic bacilli other than *E. coli,* gram-positive cocci, and bacterial strains that normally lack uropathogenic properties.[5,14] In patients that have a septic peritonitis associated with a urinary tract disorder, the visceral and parietal peritoneum provides a large surface area for absorption of bacteria and endotoxins, resulting in septic shock.[21]

Development of a UTI and subsequent urosepsis in both human and veterinary patients often represent a balance between the quantity and pathogenicity of the infectious agents and host defenses. Local host defense mechanisms, including normal micturition, extensive renal blood supply, normal urinary tract anatomy (i.e., urethral length and high-pressure zones within the urethra), urethral and ureteral peristalsis, mucosal defense barriers, antimicrobial properties of the urine, and systemic immunocompetence, are the initial defenses that prevent ascending infection.[10,12] Systemic defenses are important in preventing hematogenous spread from the urinary tract.[10] A patient with a UTI and a risk factor such as an anatomic abnormality, urinary tract obstruction, nephrolithiasis, prior urinary tract disease, renal failure, neurologic disease, diabetes, Cushing disease, or immunosuppression has a complicated UTI and is more prone to urosepsis.[2,5,10,22-24] Additionally, UTIs diagnosed in pregnant or intact dogs and cats should be considered complicated.

Clinical and laboratory findings in a patient diagnosed with urosepsis are often similar to those found in a patient whose sepsis originated from another source. These may include lethargy, fever or hypothermia, hyperemic mucous membranes, tachycardia, tachypnea, bounding pulses, positive blood culture results, and a leukogram that reveals leukocytosis or leukopenia with or without a left shift (see Chapter 106, Sepsis).[25] In patients with urosepsis, however, early laboratory tests may identify abnormalities specifically related to the urinary tract, including azotemia, active urine sediment formation, and a positive urine culture result. It is important to perform blood cultures in these patients to confirm that the organism in the urinary tract is identical to that in the blood.[6] In cases of severe sepsis, multiple organ dysfunction may be present along with pale mucous membranes, weak pulses, and prolonged capillary refill time. Additionally in cats, diffuse abdominal pain, bradycardia, anemia, and icterus may be identified.[25]

Although treatment protocols vary in these patients depending on the source of the infection and the complications resulting from sepsis, aggressive treatment is necessary. Treatment often includes a combination of intravenous fluids and broad-spectrum antimicrobial therapy. Once the culture and sensitivity information is available, antibiotic coverage should be changed if necessary, to appropriately treat the isolated organism(s). Additionally, the clinician should address the underlying condition and attempt to correct any complicating factors.[14] Although there is some overlap in the clinical presentation for various causes of urosepsis in the veterinary patient, some clinical findings, laboratory results, and treatments are unique to each condition. The rest of this chapter discusses causes of urosepsis that have been identified in veterinary medicine.

114.4 CAUSES OF UROSEPSIS

114.4.1 Pyelonephritis

The kidneys and ureters are affected more commonly by ascending bacteria than via hematogenous infections. Renal trauma or a urinary tract obstruction may increase the incidence of hematogenous spread of infection to the urinary tract because of interference with the renal microcirculation.[26,27] In human patients, hematogenous pyelonephritis occurs most commonly in those who are debilitated from chronic illness or those receiving immunosuppressive therapy.[13] Urosepsis resulting from pyelonephritis has been reported uncommonly in the veterinary literature. In a retrospective study evaluating 61 dogs with severe sepsis, a renal abscess in conjunction with pyelonephritis was the source of the infection in only three dogs.[9] In a second retrospective study evaluating 29 cats with sepsis, pyelonephritis was the cause of sepsis in only two cats.[25] The author has identified seven cats with obstructive calcium oxalate urolithiasis that were also diagnosed with pyelonephritis based on a positive bacteriologic culture result from urine collected by pyelocentesis (unpublished results). None of the identified cats were septicemic. In humans, patients with infected stones or renal pelvic urine were at greater risk for urosepsis than those with a lower tract UTI.[28]

Dogs and cats with pyelonephritis and urosepsis may be febrile, anorexic, lethargic, dehydrated, and have a history of recent weight loss. If the disease is acute, one or both kidneys may be enlarged and painful, and the animal may have signs of polyuria, polydipsia, and vomiting. Azotemia secondary to renal failure may be present, and blood work often reveals a neutrophilic leukocytosis with a left shift and a metabolic acidosis. In both acute and chronic cases, abdominal ultrasonography, intravenous pyelography, or both, may reveal mild to moderate pelvic dilation and ureteral dilation. The renal cortex and the surrounding retroperitoneal space may be hyperechoic. Renal enlargement often is identified in cases of acute pyelonephritis, and poor corticomedullary definition, distortion of the renal collecting system, and an irregular renal shape and reduced size may be seen with chronic cases. The urinalysis may reveal impaired urine concentrating ability, bacteriuria, pyuria, proteinuria, hematuria, and white blood cells or granular casts.[10,29]

As previously mentioned, treatment includes removal of predisposing factors, intravenous fluid administration, and broad-spectrum antibiotic therapy until a specific organism is identified. Antibiotic therapy targeted against the isolated organism should continue for 4 to 8 weeks. A urinalysis and culture should be performed after 1 week of treatment and before antibiotic therapy is discontinued to determine whether the infection has resolved. 491
Additionally, a urine culture should be performed 2 to 3 days after therapy has been discontinued. In animals 492

with unilateral advanced pyelonephritis, pyonephrosis, or a renal abscess, partial or total nephrectomy in addition to antibiotic therapy is the treatment of choice.[30]

114.4.2 Bladder Rupture

Although rare, urosepsis may result from a bladder or proximal urethral rupture in a patient with a UTI.[31] Urosepsis is not typically identified in patients with an intact lower urinary tract.[10] Rupture in dogs and cats most commonly occurs following blunt trauma secondary to being hit by a car. Other causes include penetrating injuries, aggressive urinary catheterization, rupture secondary to prolonged urethral obstruction, or excessive force during bladder expression. Physical examination may reveal dehydration, lack of a bladder on abdominal palpation, fluid accumulation within the peritoneal cavity, and ventral abdominal bruising. Clinical signs are often vague initially, but they can worsen as the uremia progresses and sepsis worsens. Signs may include vomiting, anorexia, depression, and abdominal pain. Abdominocentesis and abdominal fluid-to-peripheral blood creatinine or potassium ratios are often diagnostic of uroperitoneum,[32,33] and the presence of bacteria on cytologic analysis confirms a septic peritonitis.[34] Urosepsis following bladder rupture is reported uncommonly in the veterinary literature. In a retrospective study evaluating 23 dogs and cats with septic peritonitis, only one cat had septic peritonitis associated with intestinal herniation and bladder rupture.[35] In a second study evaluating 26 cases of uroperitoneum in cats, aerobic bacterial cultures were obtained from the peritoneum or bladder of five patients and, of those, three were positive. Organisms isolated included *Enterococcus, Staphylococcus,* and *α-Streptococcus*. [32]

In animals with septic peritonitis, early repair or urinary diversion, or both, is recommended to halt continued accumulation of septic urine in the abdominal cavity. The bladder defect is debrided of any devitalized tissue and then closed using a single-layer appositional suture pattern. If concerns exist regarding tissue viability of the bladder wall, a closed indwelling urinary catheter system can be used to maintain bladder decompression postoperatively. In patients with urethral trauma, treatment options include primary urethral repair, placement of a urethral catheter to stent the urethra, placement of a cystostomy tube for urinary diversion until the urethra heals, or the combination of a cystostomy tube and a urethral catheter.

114.4.3 Prostatic Infection

In addition to normal host defense mechanisms previously mentioned, prostatic fluid contains a zinc-associated antibacterial factor that is an important natural defense mechanism. Despite these defense mechanisms, bacterial colonization of the prostate can occur from ascension of urethral flora or by hematogenous spread.[36]

Suppurative prostatitis and prostatic abscess formation are some of the most common causes of urosepsis in canine surgical patients, with 12 of 61 cases diagnosed in one study.[9] Dogs with suppurative prostatitis usually have a history of an acute onset of illness. Patients can present with signs of anorexia, vomiting, tenesmus, lethargy, fever, dehydration, injected mucous membranes, weight loss, pain on rectal examination, caudal abdominal discomfort, and pain in the pelvic and lumbar regions.[37-39] Additionally hematuria, pyuria, stranguria, hemorrhagic preputial discharge, urinary incontinence, or the inability to urinate can also be identified.

If the infection is not treated, microabscesses can form, and these can eventually coalesce into a large abscess. Septicemia and endotoxemia quickly develop, particularly if the abscess has ruptured into the abdominal cavity.[40] In dogs with rupture of a prostatic abscess, the peritoneal surface provides a large area for absorption of bacteria and bacterial by-products, providing conditions favorable for septic shock. Hind limb edema has also been identified in these patients and can result from altered vascular permeability secondary to sepsis, as well as from an abscess that interferes with normal lymphatic and venous drainage from the pelvic limbs.

A definitive diagnosis of prostatic infection is confirmed following identification of septic exudate from a prostatic wash, traumatic catheterization, urethral discharge, or fine-needle aspirate. Owing to the nature of the problem, it is difficult and even clinically dangerous to try and collect prostatic fluid from dogs with acute prostatitis.[38] In dogs, as in humans with acute bacterial prostatitis, bacteremia may result from manipulation of the inflamed gland.[13,38] Because the infectious agent often can be identified on a Gram stain and culture of the urine, vigorous prostatic palpation is avoided.[13] Abdominal ultrasonography may reveal varying echogenicity of the gland with symmetric or asymmetric enlargement. Cystlike structures may also be present and may represent abscess formation. It is important to note that dogs with prostatitis may have normal ultrasonographic examination findings, underscoring the need to make a definitive diagnosis using the previously mentioned techniques.

Suppurative prostatitis and prostatic abscesses are serious life-threatening disorders. In patients with acute suppurative prostatitis, treatment involves intravenous fluid therapy to correct dehydration and treat cardiovascular shock, and antibiotic therapy based on culture and sensitivity results of the organisms found in prostatic fluid. Antibiotics should be administered for a minimum of 4 to 6 weeks. The urine or prostatic fluid should be cultured following discontinuation of antibiotic therapy, and again in 2 to 4 weeks to determine if the infection has been eliminated.[36-38] If the infection has not been eliminated, resistant bacterial infections of both the prostate and urinary tract can develop. Castration is recommended and appears to be beneficial in the resolution of chronic bacterial prostatitis in an experimental model.[38,41]

In addition to the previously-mentioned interventions, surgical drainage or excision is often the treatment of choice in a patient with a prostatic abscess. Antimicrobial therapy in conjunction with castration has been ineffective for resolving abscesses.[39] Before surgery, ultrasonography is used to determine the location(s) of the abscess(es). Surgical techniques that have been described to treat prostatic abscess formation include prostatic omentalization, placement of Penrose drains, marsupialization of the abscess, ultrasonographically guided percutaneous drainage, and subtotal or excisional prostatectomy.[37,42,43] In one study, of three dogs with prostatic abscesses, two had signs of sepsis.[42] In a second study, 15 of 92 dogs died during the postoperative period because of sepsis. *E. coli* was the most common bacterial isolate.[40] Sepsis and shock were common postoperative complications, developing in 33% of the dogs surviving surgery. Absorption of bacteria and toxins 492 from both an 493 infected prostate gland and inflamed peritoneal surface contributed to septic shock.[40] In approximately half of the dogs that died from septic shock, the abscess ruptured before surgery was performed.

114.4.4 Pyometra

Urosepsis can occur in both dogs and cats diagnosed with pyometra, with or without uterine rupture. In the largest retrospective study to date evaluating sepsis in the small animal surgical patient, pyometra was the most common source of urosepsis, occurring in 14 of 61 dogs reported. Of 4 cats included in the study, urosepsis occurred secondary to a pyometra in 1 cat and a ruptured uterus in a second cat.[9] In a review of 80 cases of pyometra, 3 of 73 dogs developed complications from generalized septicemia and thromboembolic disease during the immediate postoperative period, and 1 dog died from endotoxic shock due to a ruptured uterus.[44] In a second retrospective study evaluating 183 cats diagnosed with pyometra, uterine rupture was diagnosed in 7, with fatal septic peritonitis diagnosed in 4.[45]

Although many aerobic and some anaerobic bacteria have been identified in both dogs and cats with pyometra, including *Staphylococcus*, *Streptococcus*, *Pasteurella*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Aerobacter*, *Haemophilus*, *Moraxella* spp, and *Serratia marcescens*, *E. coli* is the bacterium that is isolated most commonly. Although culture results are rarely negative in the dog, aerobic culture results in cats are negative 15% to 31% of the time.[45,46]

Dogs diagnosed with a pyometra are often systemically sick with signs of anorexia, lethargy, depression, polydipsia, vomiting, diarrhea and, if the cervix is patent, a malodorous vaginal discharge. When abdominal pain is present, septic peritonitis is likely.[45] Body temperature may be normal, elevated, or subnormal. Clinical signs in cats are similar, but often are more subtle.

Clinicopathologic abnormalities in both species can occur to varying degrees and may include anemia, leukocytosis, or leukopenia with a left shift, azotemia, hypoalbuminemia, hypoglycemia or hyperglycemia, hyperglobulinemia, increased alkaline phosphatase levels, and acidosis.[45,47-49] Before surgery, medical therapy is instituted and includes intravenous fluid and antibiotic therapy (see Chapters 65 and 106, Shock Fluids and Fluid Challenge and Sepsis, respectively). Electrolyte, acid-base, and/or clotting abnormalities should be addressed as soon as possible. Surgery is not postponed in very sick animals for more than a few hours because of the continued bacteremia and septicemia that is occurring. Treatment for pyometra is ovariohysterectomy. If the uterus ruptures during surgery, the abdomen is lavaged and the patient treated for septic peritonitis (see Chapter 133, Peritonitis).

114.4.5 Catheter-Associated Urinary Tract Infection

In human patients, bacteriuria occurs in up to 20% of hospitalized patients with indwelling urinary catheters and, of these patients, 1% to 2% will develop gram-negative bacteremia.[13] The catheterized urinary tract has repeatedly been demonstrated to be the most common source of gram-negative sepsis in human patients,[13] and although the condition is rare, the mortality rate of these patients can reach 30%.[13] In human patients, bacteremia can occur immediately as a result of mucosal trauma associated with catheter placement and removal or secondary to mucosal ulceration.[13] Many infecting strains, including *E. coli, Proteus, Pseudomonas, Klebsiella,* and *Serratia* show marked antimicrobial resistance compared with organisms identified in an uncomplicated UTI.

Although nosocomial UTIs following the use of an indwelling urinary catheter is reported to be a common complication in both dogs and cats, subsequent development of urosepsis is uncommon. Bacterial UTIs developed in 20% of healthy adult female dogs after intermittent urinary catheterization, in 33% of male dogs during repeated urinary catheterization, and in 65% of healthy male cats within 3 to 5 days of open indwelling urinary catheterization.[10,50]

A few studies in the veterinary literature have looked at the incidence of UTIs in dogs and cats when a closed catheter system was used. In one study, 11 of 21 (52%) animals and, in a second study, nine of 28 animals (32%) developed catheter-associated infections.[51,52] Both of these studies suggested that the risk of infection increased with duration of catheterization and that antibiotic therapy was associated with increasingly resistant gram-negative organisms. Although the incidence of catheter-associated infections was high in both studies, urosepsis was not identified. In a study looking at the incidence of catheter-associated UTIs in a small animal intensive care unit, only four of 39 dogs (10.3%) developed a UTI.[52] The lower incidence reported in this study was attributed to a shorter duration of catheterization and stricter definitions for infection, indications for catheterization, urine sample collection, and protocol for catheter placement and maintenance. Urosepsis was not a reported complication.

In both veterinary and human hospitals, pathogens can be introduced from the hands of hospital staff via instrumentation or from contaminated disinfectants. The most common locations for bacteria to enter the system are the catheter-collecting tube junction and the drainage bag port. Intestinal flora can migrate along the catheter into the bladder from the perineal area of the patient.[13] To prevent or minimize the incidence of catheter-associated infections, clinicians should avoid indiscriminate use of catheters. Additionally, catheters should be used cautiously in patients with preexisting urinary tract disease, those undergoing diuresis, and those whose immune system is compromised. A sterile closed collection system, as well as appropriate antimicrobial therapy if an infection is present, are also recommended. Because a longer duration of catheterization has been associated with antimicrobial-resistant bacteria and because one cannot predict the duration of catheterization, prophylactic use of antimicrobial agents is not recommended.[52] Additionally, diagnostic and therapeutic procedures that may result in the introduction of bacteria into the urinary system should also be minimized.[10,13]

114.5 CONCLUSION

Urosepsis is diagnosed uncommonly but is a serious problem that can affect both dogs and cats. Conditions in veterinary medicine that have been associated with urosepsis include bacterial pyelonephritis and renal abscess formation, bladder rupture in patients with a UTI, prostatic suppuration and abscess formation, testicular and vaginal abscess formation, pyometra, and catheter placement. Risk factors for urosepsis that may complicate treatment include an anatomic abnormality, urinary tract obstruction, nephrolithiasis, prior urinary tract disease, 493
renal failure, neurologic disease, diabetes, hyperadrenocorticism, and immunosuppression. Accurate recognition 494
and aggressive therapy addressing the underlying condition, complicating risk factors, and the associated inflammatory response are necessary to prevent significant morbidity and mortality.

114.6 SUGGESTED FURTHER READING*

JW Bartges: Urinary tract infections. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. 2005, Elsevier, St Louis, *Book chapter focusing on UTIs in both dogs and cats. Contains good information on natural and acquired host defenses of the urinary tract as well as virulence factors.*

EM Hardie, CA Rawlings, CA Calvert: Severe sepsis in selected small animal surgical patients. *J Small Anim Pract*. **44**, 2003, 13, *A retrospective review of severe sepsis in the small animal surgical patient looking at 61 dogs and 4 cats, with identification of the urogenital tract as the source of infection in approximately one half of the cases.*

CM Kunin: Definition of acute pyelonephritis vs the urosepsis syndrome. *Arch Intern Med*. **163**, 2003, 2393, *A short communication in response to an article on acute pyelonephritis suggesting that a more appropriate term for the condition affecting the patients described in the article would be* urosepsis syndrome.

MA O'Donnell: Urological sepsis. In SR Zinner (Ed.): *Sepsis and multiorgan failure*. 1997, Williams & Wilkins, Baltimore, *A good review chapter on urologic sepsis in human patients.*

SD Smarick, SC Haskins, J Aldrich, et al.: Incidence of catheter-associated urinary tract infection among dogs in a small animal intensive care unit. *J Am Vet Med Assoc*. **224**, 2004, 1936, *A paper looking at the incidence of catheter-associated UTI among dogs in a small animal intensive care unit. A lower incidence of catheter-associated urinary infections was found than in previous veterinary studies. Lower incidence*

attributed to a shorter duration of catheterization, stricter definition of infection, indications for catheterization, urine sample collection, and the protocol for catheter placement and maintenance. Urosepsis not a reported complication.

* See the CD-ROM for a complete list of references

115 Chapter 115 Necrotizing Soft Tissue Infections

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115.1 KEY POINTS

- Necrotizing fasciitis (NF) and streptococcal toxic shock syndrome (STSS) can be rapidly fatal if not identified and managed aggressively.
- Signs of circulatory shock must be managed rapidly using fluid resuscitation and analgesia.
- Because of the lack of obvious skin changes in many cases of NF, a high index of suspicion is necessary for diagnosis.
- Surgery is the cornerstone to management of NF, and radical debridement including amputation may be necessary to eliminate the infection.
- Antibiotic usage should be broad spectrum until directed by culture and sensitivity results.
- If a virulent streptococcal infection is suspected, fluoroquinolone antibiotics should not be used.

115.2 INTRODUCTION

Multisystemic streptococcal toxic shock syndrome (STSS) and locally invasive necrotizing fasciitis (NF) are rapidly progressive diseases associated with virulent group A streptococcal infections in people. NF in humans has also been referred to as *flesh-eating disease, hemolytic streptococcal gangrene,* and *suppurative fasciitis*. [1] Similar clinical pictures have been described in dogs and cats, caused by infection with various *Streptococcus canis* isolates and other group G streptococci.[2-5] Clinical features of STSS include a streptococcal infection from a normally sterile site occurring concomitantly with signs of circulatory shock and two or more of the following: renal dysfunction, coagulopathy, hepatic dysfunction, acute respiratory distress syndrome, soft tissue necrosis, and erythematous rash.[6] It is differentiated from other invasive streptococcal infections because of the early occurrence of shock and multiorgan failure. Clinical features of NF in dogs and cats include necrosis of soft tissue involving the fascial planes and either death, circulatory shock, disseminated intravascular coagulation, organ dysfunction, or isolation of hemolytic streptococci from a normally sterile site.

Human mortality rates for NF range from 6% to 76%, with an average fatality rate of 37%.[7] Case mortality rate for STSS is reported to be 30%.[6] Mortality rates in cats and dogs with virulent streptococcal infections cannot be calculated accurately from the few case reports available. Risk factors identified in human medicine include age over 50 years, atherosclerosis or peripheral vascular disease, obesity, trauma, hypoalbuminemia, diabetes mellitus, and glucocorticoid usage.[1,7] None of the reported animal cases noted an immunocompromised state.

Most of the veterinary cases of NF report a history of minor trauma and presumed inoculation of virulent bacteria.[3-4] Infection can spread rapidly, and seemingly limited infections can cause limb-threatening and life-threatening systemic sequelae.[8] Fibrous attachments between the subcutaneous and fascial tissue can form a boundary to limit spread of organisms, however such boundaries do not exist in the extremities or truncal regions, making these areas more susceptible to widespread infection and NF.[9-10]

Despite their severity and rapid progression, relatively little is actually known about the pathophysiology of STSS and NF. Enhanced toxicity of virulent streptococci may occur through massive cytokine release and induction of a systemic inflammatory response and septic shock.[11] Expression of bacterial hyaluronidase will also degrade fascia.[12] Angiothrombotic microbial invasion with liquefactive necrosis of the superficial fascia is a key pathologic process of NF. Occlusion of nutrient vessels can lead to extensive undermining of apparently normal-appearing skin, followed by gangrene of the subcutaneous fat, dermis, and epidermis, evolving into ischemic necrosis.[1]

115.3 DIAGNOSIS

When the possibility of a virulent streptococcal infection exists, rapid therapeutic and diagnostic intervention is necessary to limit morbidity and prevent mortality. STSS is associated with streptococcal toxins invading the circulatory system through the skin barrier or via organ infections, such as pneumonia or urinary tract infections. Fever and signs of malaise may be described by the pet owner, and clinical signs of circulatory shock may be evident on physical examination.

The clinical signs of NF can be very nonspecific. Surgery may have been performed recently, or the pet owner may have witnessed a traumatic event or discovered a skin lesion. The owners may also describe the pet having general signs of malaise or lameness. Initial intervention may be for presumed pain or severe bruising. Most patients have signs that include fever and circulatory shock. Affected tissue may show signs of bruising, cellulitis, and crepitus from subcutaneous emphysema (Color Plate 115-1). Cutaneous bullae are considered an important indicator of impending dermal necrosis in humans; however, this has not been a frequent finding in veterinary patients.[4,6] Although a skin wound or discoloration is obvious, the epidermis can appear unscathed with deep tissue necrosis. When skin lesions are seen, they should be outlined with a marker so that progression of the discoloration can be followed. Protective gloves should be worn during examination of the lesions and patient handling to prevent inadvertent contamination of a cut on the examiner's hand with potentially virulent pathogens.

Intense pain focused around the affected area is considered a hallmark of NF in humans. Pain may be disproportionate to the appearance, because the originating site may not be as painful as the surrounding tissue. When clinical signs of circulatory shock and pain are present, rapid resuscitative techniques and analgesia are provided before additional diagnostic evaluation is carried out.

115.3.1 Laboratory Findings

Laboratory findings cannot be used reliably to diagnose NF or STSS, but they may reflect changes associated with infection and a systemic inflammatory response syndrome. These may include hemoconcentration, hypoalbuminemia, neutrophilia or neutropenia, left shift, hyperlactatemia, coagulation alterations consistent with DIC, hypoglycemia, elevated creatinine phosphokinase levels, and organ dysfunction (elevated serum alanine transaminase, alkaline phosphatase, bilirubin, creatinine levels). Hypocalcemia can occur when extensive fat necrosis has developed with NF.[7]

When signs of STSS are evident, the source of infection must be determined. Urinalysis may show evidence of infection confirmed with culture analysis. When thoracic radiographs suggest pneumonia, transtracheal wash samples may indicate infection. Blood cultures may grow infectious organisms. Cytologic evaluation of a fine-needle aspirate from an affected tissue site or organ may reveal a discharge, with or without evidence of chains of cocci.

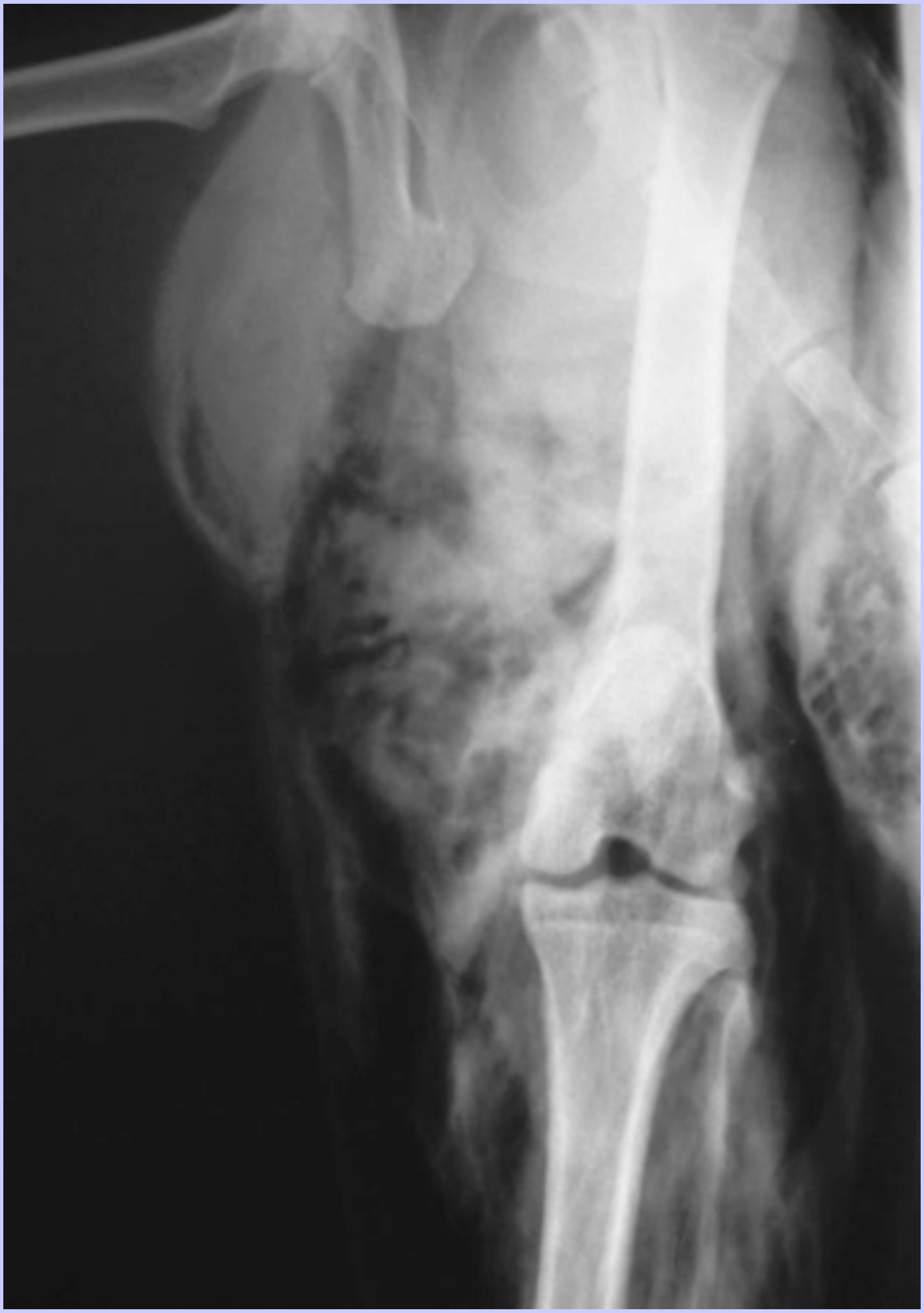
115.3.2 Imaging

Imaging studies are suggestive but not specific for NF. Radiographs of the affected region may show soft tissue swelling and, rarely, subcutaneous air (Figure 115-1). Computed tomography features suggestive of NF include deep fascial thickening, enhancement, fluid, and gas in the soft tissue planes in and around superficial fascia.[13] On computed tomography, fascial thickening, fascial stranding, and asymmetric thickening of fascial plans may be seen. Magnetic resonance imaging may prove helpful in determining the extent of deep tissue infections not readily identified from the skin surface because of its soft tissue and multiplanar imaging capabilities. Absence of deep fascial involvement can exclude NF. However, magnetic resonance imaging cannot differentiate necrotizing infections from nonnecrotizing problems, and the time involved in obtaining test results may delay surgery.[14]

115.3.3 Definitive Diagnosis

Definitive diagnosis of STSS requires positive streptococcal culture findings and evidence of septic shock. Definitive diagnosis of NF is based on the histopathologic findings of fascial necrosis and myonecrosis. Frozen section biopsy can provide a rapid diagnosis at the time of surgical exposure. Because of the rapid progression of disease and the delay in obtaining results, treatment must begin before culture or histopathology results are confirmed. 495 496

Figure 115-1 Radiographs of necrotizing fasciitis may demonstrate soft tissue swelling and occasionally subcutaneous emphysema. The extent of the necrosis may not be reflected by the size of the skin lesion.



115.4 TREATMENT

Successful management of STSS and NF is based on treatment of the entire patient, not just the infected site. Patients in circulatory shock are resuscitated rapidly using large-volume resuscitation techniques with a combination of balanced isotonic crystalloid fluids and synthetic colloids (e.g., hetastarch).[15] Resuscitation is done before diagnostics when perfusion abnormalities exist. Fluids are titrated to perfusion end points, namely, normal heart rate, blood pressure, mucous membrane color, and capillary refill time. Heart rate may not return to normal until analgesics are administered. Because of the high degree of pain associated with NF, strong analgesic intervention is necessary (see Anesthesia and Pain Management section). Injectable opioid agonists (e.g., hydromorphone, oxymorphone) in combination with regional or local anesthesia may be adequate. Opioids can be continued as a constant rate infusion in combination with low-dose ketamine and lidocaine to provide continuous analgesia. Nonsteroidal antiinflammatory analgesic medications are not recommended until signs of circulatory shock have been alleviated and debridement has been successful.

Glucose is administered as a bolus followed by a continuous rate infusion when hypoglycemia is present. Calcium is administered when plasma levels are significantly decreased. Plasma transfusion may provide coagulation factors and antithrombin when DIC is suspected. Intravenous immunoglobulin G therapy has shown some benefit in clinical improvement and reduction in mortality in treated versus control human patients.[16] It may also reduce the need for radical debridement in cases of NF.[17] Its use in veterinary medicine for STSS or NF has not been established.

115.4.1 Antibiotic Therapy

After fine-needle aspirate samples for cytology, Gram stain, and aerobic, anaerobic, and fungal culture of the affected area have been collected, injectable broad-spectrum antibiotic coverage can be instituted.[4,18] Culture and sensitivity samples should always be acquired at the start of medical treatment as well as during the debridement procedure. Penicillin G, aminopenicillins (ampicillin, amoxicillin), and cephalosporins will target gram-positive organisms and many gram-negative organisms. Aminoglycosides and third-generation cephalosporins may increase gram-negative coverage, and clindamycin or metronidazole provide anaerobic coverage. Gentamicin has a synergistic effect with penicillin against streptococci. In addition to microbial killing, clindamycin may also suppress bacterial toxin synthesis, inhibit streptococcal M-protein synthesis (which will facilitate mononuclear phagocytosis), and suppress lipopolysaccharide-induced monocyte synthesis of tumor necrosis factor.[19] Fluoroquinolone administration, specifically enrofloxacin, is not recommended, because it may have limited activity against streptococcal infection and may cause bacteriophage-induced lysis of *S. canis,* enhancing its pathogenicity.[20]

115.4.2 Surgical Debridement

The most important part of NF treatment is surgical debridement. Because of the underlying loss of blood supply and necrosis, systemic antibiotic therapy cannot yield adequate tissue levels of antibiotics. Persistent necrotic tissue serves as a culture medium, creating an anaerobic environment that impairs polymorphonuclear cell activity. The diseased tissue must be excised. Therefore inadequate debridement will result in further progression of necrosis.

Once the patient is cardiovascularly stable, surgical debridement and additional sample collection are performed. Because of the insidious and aggressive nature of NF, surgical intervention should occur within 4 to 6 hours of presentation. Higher amputation and mortality rates have been documented in humans when surgery was delayed more than 12 hours.[21-22]

Surgical preparation should include a generous area surrounding the affected tissue, because significant undermining of the tissue planes may not be evident until surgical exposure. Controlled surgical debridement of necrotic and diseased tissue is the cornerstone of treatment and a determinant of increased survival. Successful debridement may require multiple procedures, not just a single surgery. Because of the lack of purulent discharge, typical drainage techniques are ineffective. There are no large pockets of purulent material for drain placement. Therefore appropriate debridement requires removal of large amounts of tissue.

Exposure of viable tissue may involve resection of muscle and tendons. Muscle viability can be tested by its response to stimulation from an electrocautery device. When contraction is absent, the muscle may not be viable and should be debrided. If the wound is on the limb, debridement can result in loss of limb function. Therefore amputation may be the best option for limiting morbidity and mortality. This is a difficult emotional decision for the owner. Often the pet has deteriorated in such a rapid fashion that the owner may not understand the necessity for an amputation. Because a delay can result in loss of the pet, appropriate client communication to emphasize the severity and rapid progression of NF is essential.

115.4.3 Postoperative Care

Postoperative monitoring should follow Kirby's Rule of 20 (see Chapter 201, Daily Assessment of the Critically Ill Patient).[23] Crystalloid and colloid fluids are continued to maintain intravascular volume and replace ongoing fluid losses. The cardiovascular system is monitored closely for decompensation, and frequent evaluation of glucose, albumin, and electrolyte levels will uncover any abnormalities that require intervention. Evaluation of the wound edges is done frequently (initially every 30 to 60 minutes) to determine if necrosis is continuing to spread despite surgery, indicating the need for repeat debridement. Antibiotic therapy is adjusted once culture and sensitivity results are available. Special attention is paid to providing adequate nutrition and analgesia.

Nutritional support is an important consideration, because these patients have increased protein loss in the exudates and increased demands of healing (see Chapter 202, Nutritional Assessment). There may also be a decrease in voluntary food intake associated with pain or fever. Partial parenteral nutrition or enteral feeding via nasogastric or esophagostomy tube will facilitate protein metabolism and limit protein catabolism during 496 recovery. Caloric requirements should be calculated 497 and then nutritional supplementation started immediately postoperatively, with full caloric supplementation reached within 48 hours.

115.4.4 Hyperbaric Oxygen

Hyperbaric oxygen therapy is the delivery of oxygen at higher than atmospheric pressure. Commonly, this involves delivery of 100% oxygen at 2 to 2.5 standard atmospheres for 90 minutes every 8 hours, then twice daily until there is no evidence of ongoing necrosis. Hyperbaric oxygen therapy delivers significantly higher levels of dissolved oxygen to tissues. It is theorized that higher plasma oxygen levels will support tissue that has experienced vascular compromise. Additionally, hyperbaric oxygen therapy may enhance host antimicrobial activity and the action of various antibiotic agents by facilitating their transport across the bacterial cell wall.[24] Unfortunately, most research in this area is either anecdotal or has yielded conflicting results.[4,25-26] There are no controlled veterinary studies demonstrating efficacy of hyperbaric oxygen in NF, but it has been described in a single canine case of limb NF.[4]

115.5 CONCLUSION

STSS and NF can be treated successfully if medical and surgical therapy are provided rapidly. A delay in therapy will worsen the prognosis. Circulatory shock and laboratory abnormalities are corrected immediately and aggressive analgesia provided. Surgery with radical debridement is required for successful treatment of NF. The extent of the lesion may not be fully appreciated until surgery is performed. Amputation or multiple surgical procedures may be necessary to remove diseased tissue. Major reconstructive procedures may be required once diseased tissue has been successfully removed.

115.6 SUGGESTED FURTHER READING*

R Kirby, E Rudloff: Crystalloid and colloid fluid therapy. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, Philadelphia, *A description of the clinical use of crystalloid and colloid fluids for resuscitation from shock.*

CW Miller, JF Prescott, KA Mathews, et al.: Streptococcal toxic shock syndrome in dogs. *J Am Vet Med Assoc*. **209**, 1996, 1421, *A study that prospectively examines a series of dogs with necrotizing streptococcal infections*.

D Purvis, R Kirby: Systemic inflammatory response syndrome: septic shock. *Vet Clin North Am Small Anim Pract*. **24**, 1994, 1225, *Article that describes the pathophysiologic findings in SIRS and septic shock, and describes 20 clinical parameters that should be monitored closely in patients with severe disease*.

* See the CD-ROM for a complete list of references

116 Chapter 116 Catheter-Related Bloodstream Infection

Sean Smarick, VMD, DACVECC

116.1 KEY POINTS

- Intravenous catheters may become contaminated and can lead to local and distal infectious complications. A bacteremia caused by a colonized catheter is referred to as a *catheter-related bloodstream infection (CRBSI)*.
- The diagnosis of a CRBSI includes culturing the catheter or blood or both, but any fever of unknown origin, bacteremia, or infection at the insertion site should prompt the clinician to consider a CRBSI.
- Treatment of known CRBSI includes removing the catheter and administering systemic antibiotics.
- Frequency of CRBSI may be reduced by aseptically placing and maintaining catheters and educating caretakers involved in catheter placement.

116.2 DEFINITION

Intravenous catheters are often used in critically ill patients, but they can become contaminated with microorganisms. Skin contaminants may be introduced during placement or may migrate along the external surface of the catheter. Additionally, contamination of the catheter hub or infusate may lead to colonizing of the internal surface. Some bacteria produce biofilm, a matrix of microorganisms and their produced glycocalyces along with host salts and proteins that provide protection from the host's defenses. Catheter contamination may lead to local signs of phlebitis; when catheter colonization leads to a bacteremia, the resultant infection is referred to as a *catheter-related bloodstream infection (CRBSI)*. [1,2]

116.3 INCIDENCE

CRBSI has been reported in dogs and cats. In small animal intensive care units, CRBSIs have been implicated as a cause of morbidity and mortality.[3-7] In veterinary medicine the incidence of catheter contamination has been reported as 10.4% to 22% in peripheral catheters[3,7,8] and from 0 to 26% in jugular catheters, which is consistent with human reports.[6,7,9] CRBSI is well studied in humans, and the incidence is approximately 5% with central venous catheters.[10] In a few prospective studies in veterinary medicine, the incidence in small animals has been reported as 1 in 88 with peripherally placed 8-inch and 12-inch catheters,[3] 1 in 65 in similar catheters placed in the jugular vein,[6] 0 in 30 in jugular catheters in cats,[9] and 2 in 121 with both peripheral and centrally placed catheters.[7] This approximates to a combined rate of 1.3% (bloodstream infections per 100 catheters). This rate likely underestimates the current and future incidence of CRBSI, because peripheral venous catheters have a lower rate of CRBSI, and the use of central venous and arterial catheters is increasing in veterinary medicine. Indwelling catheters that are tunneled through the subcutaneous tissues have been described for long-term use (weeks to months) in veterinary patients. Some of these catheters have access ports also placed subcutaneously. The combined reported rate of CRBSI for these types of catheters of 2 in 60 is consistent with rates reported in people for similar types, despite a decreased duration of catheterization in the veterinary patients. The veterinary population was overrepresented by patients undergoing radiation therapy for neoplasia, and that group included both of the patients that developed CRBSI.[11-13]

116.4 DIAGNOSIS

CRBSI should be considered in febrile patients that have an intravascular catheter in place when there is no other obvious source of infection. Phlebitis and, especially, purulent discharge at the catheter site may indicate that catheter colonization has resulted in a localized infection that may lead to a CRBSI; however, the lack of localized reaction does not rule out a CRBSI, because close to 50% of humans show no local signs. Because clinical signs are not reliable, cultures are required for the diagnosis of a CRBSI.[1,14] It should be noted that a CRBSI differs from a catheter-associated bloodstream infection. In a CRBSI, the catheter is the primary source of infection whereas in a catheter-associated bloodstream infection, a catheter is seeded and colonized by organisms spread hematogenously from another source of infection. The lack of an identifiable or suspected source of infection and critical interpretation of cultures are needed to diagnose a CRBSI.[14]

Considering the relatively low incidence of CRBSI, routine screening of qualitative (i.e., positive versus negative) catheter tip or segment cultures is not recommended because of the number of false-positive results.[14,15] Numerous culturing methods of diagnosing a CRBSI have been reported and the source (intraluminal versus extraluminal) of the infection, number of lumens of the catheter, availability of culturing methods, ability to aspirate the catheter, and need to keep the present catheter in place may dictate which method is to be used in individual patients. Because infections identified soon after catheter placement tend to originate on the external surface, and infections 498 of long-term catheters tend to originate on the internal lumen, culturing 499 blood from the lumen may be a source of false-negative cultures in short-term catheterization.[14] Multilumen catheters pose a challenge in that one or multiple lumens may be colonized, leading to false-negative results if only one lumen is cultured. In one study involving humans, sampling only one lumen of a triple-lumen catheter identified only 60% of the CRBSIs.[16] Catheters do not necessarily need to be removed to diagnose a CRBSI. Considering the low number of true CRBSIs in febrile patients, catheters in such patients may remain unless they are no longer needed, they have a purulent discharge, or the patient is decompensating.[1,14,17]

Ideally, quantitative cultures of blood obtained percutaneously and through the catheter are obtained. A positive result is one in which the catheter-obtained culture(s) has 3 to 5 times greater bacterial concentration than the culture obtained percutaneously. Alternatively, qualitative cultures in which positive blood culture results from the catheter precede results from the percutaneous culture by more than 2 hours can be used if the quantitative methods are unavailable. If neither method is available or if the catheter is removed, a semiquantitative culture obtained by rolling a 5-cm section of the catheter four times over a blood agar plate and finding more than 15 colony-forming units (CFU) per ml is also a method with good sensitivity and specificity in humans. Qualitative or quantitative (>100 CFU/ml) blood cultures drawn from the catheter and quantitative cultures (>1000 CFU/ml) of broth that was flushed through or sonicated with the catheter have also been described for diagnosing CRBSI. Staining lysed cells from catheter-obtained blood samples with acridine orange to look for organisms and performing cultures of endoluminal brushing of the catheter also show promise as additional methods of diagnosis.[1,14]

For obtaining blood cultures, the catheter and percutaneous site should undergo aseptic preparation, equal volumes for each sample should be collected, and the samples should be obtained within 10 minutes of each other. Ideally, cultures are obtained before instituting empiric antibiotic therapy.[1,14]

116.5 TREATMENT

Treatment of known CRBSI consists of removal of the catheter and appropriate antibiotic therapy; however, in febrile patients with a catheter in place without local signs of infection, “watchful waiting” is an effective strategy. In humans, leaving the catheter in place awaiting culture resulted led to a 60% reduction in the number of catheters removed with no significant change in outcome. The risks of catheter replacement versus having a potential nidus of infection must be weighed in each patient; deteriorating patients should be treated more aggressively. When a suspected infected catheter is left in place, an antibiotic lock consisting of concentrated amounts of antibiotics, ethanol, or other substances occupying the lumen dead space has been shown in humans to effectively eliminate many bacterial infections and spares the patient the catheter removal. The concentrated amount of antibiotic allows biofilm penetration unattainable with systemic administration. The catheter should not be replaced with an over-the-wire technique; a separate insertion site should be used. Systemic antibiotics guided by culture and sensitivity should be continued for 10 to 14 days after catheter removal. As with many infections, the best treatment of CRBSI is prevention.[1,17]

116.5.1 Box 116-1 Checklist for Placement and Maintenance of Intravascular Catheters to Prevent Catheter-Related Bloodstream Infections

- Wash hands.
- Wear clean gloves.
- Provide aseptic insertion.
- Use a 2% chlorhexidine skin preparation.
- For peripheral intravenous catheters, use 3 to 7 cycles of scrub, then wipe with alcohol, and do not touch the insertion site after preparation.
- Use sterile gloves for arterial and central venous catheters and maximum barrier protection (sterile gown and drape, mask) when placing central venous catheters. Change gloves for the new catheter when rewiring.
- Minimize cutdowns.
- Dress the catheter with a sterile gauze (or Band-Aid) and bandage.
- Avoid ointments at the catheter site.

116.5.1.1 Catheter Dressings

Inspect daily.

- Change q48h or if moist or soiled.
- Wipe injection ports with alcohol before using; stopcocks should be capped.

- Change administration sets (aseptically) q72h.
- Change administration sets (aseptically) q96h if an arterial line transducer.
- Change administration sets (aseptically) q6-12h if propofol infused.
- Change administration sets (aseptically) q24h if lipid-containing TPN solutions are infused.
- Evaluate the need for the catheter; remove it when it is no longer needed.

TPN, Total parenteral nutrition.

116.6 PREVENTION

Recommendations for the prevention of CRBSI have been published in the veterinary literature and include caregiver handwashing, placement of catheters by trained personnel, aseptic catheter placement, use of the most bioinert catheter material (i.e., polyurethane versus Teflon), and monitoring for CRBSI. Scheduled catheter replacement is no longer recommended. These recommendations were based on limited veterinary observational studies and guidelines for humans.[2,6,7]

In the absence of well-controlled and well-powered veterinary studies, it is reasonable to adopt human recommendations to prevent CRBSI formulated on evidence-based guidelines. In 2002 the Centers for Disease Control and Prevention (CDC) published (and made available online) the “Guidelines for the Prevention of Intravascular Catheter-Related Infections.”[15] A checklist adapted to veterinary patients to decrease the incidence of CRBSI is presented in Box 116-1. Educating caregivers about the indications, proper placement, maintenance, and nosocomial surveillance of vascular catheters is considered paramount in preventing CRBSI. Other recommendations from the CDC include not to administer prophylactic antibiotics and not to replace catheters routinely for infection control. Catheters that were placed under less-than-ideal emergency conditions, however, should be replaced within 48 hours, and peripheral catheters may be replaced every 72 to 96 hours to prevent phlebitis.

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As with all nosocomial infections, handwashing is crucial for prevention and it should be noted that wearing gloves augments the preventive effect of but does not replace handwashing. The CDC also recognizes infusates and intravenous admixtures to be a source for CRBSI. It is recommended that blood products and lipid-containing parenteral nutrition solutions should not be infused for longer than 4 hours and 24 hours, respectively. Additionally, the sterility of administered drugs and intravenous admixtures should be maintained by using singe-dose vials, swabbing multidose vials with alcohol before aspiration, and discarding any suspected compromised solution.[15]

In the war against device-associated nosocomial infections, catheters impregnated with antiseptics and antibiotics have been introduced. In humans, studies support a reduction in the incidence of CRBSI with the use of these catheters; however, the debate over their use continues. They are not recommended for routine use because of reported allergic reactions, potential for the development of resistant organisms, and the additional expense.[1,15]

116.7 SUGGESTED FURTHER READING*

T Francey, F Gaschen, J Nicolet, et al.: The role of *Acinetobacter baumannii* as a nosocomial pathogen for dogs and cats in an intensive care unit. *J Vet Intern Med*. **14**, 2000, 177, *A retrospective study of a resistant* *organism in a veterinary intensive care unit where CRBSIs were presumed to play a role in this serious infection.*

AC Lippert, RB Fulton, AM Parr: Nosocomial infection surveillance in a small animal intensive care unit. *J Am Anim Hosp Assoc*. **24**, 1988, 148, *A prospective study of urinary and intravenous catheter-associated infections in a veterinary intensive care unit examining the need for nosocomial infection surveillance and prevention.*

* See the CD-ROM for a complete list of references

117 Chapter 117 Hypercoagulable States

Shane W. Bateman, DVM, DVSc, DACVECC

117.1 Box 117-1 Possible Causes of Disseminated Intravascular Coagulation

117.1.1 Infectious, inflammatory

Bacterial

- Severe localized bacterial infection
- Bacterial sepsis

Viral

- Infectious canine hepatitis
- Canine distemper
- Canine parvovirus
- Canine herpesvirus
- Feline infectious peritonitis
- Feline panleukopenia

Fungal

- Fulminating systemic fungal diseases
- Candida sepsis

Parasitic

- Fulminating systemic protozoal diseases

117.1.2 Noninfectious, inflammatory

Neoplastic

- Hemangiosarcoma
- Inflammatory carcinoma

  - Leukemias (especially acute)
  - Malignant histiocytosis

Tissue trauma, ischemia

  - Severe shock syndromes
  - Gastric dilation-volvulus
  - Massive crushing injury
  - Envenomation (snake, scorpion, insect)
  - Heat stroke
  - Pancreatitis

Immune-mediated causes

  - Immune-mediated hemolytic anemia
  - Hemolytic transfusion reaction

117.2 KEY POINTS

- Two types of hypercoagulable states exist: microvascular and macrovascular.
- Virchow's triad describes the three factors required for macrovascular thrombus formation: blood stasis, endothelial injury or pathology, and a hypercoagulable state.
- Microvascular thrombosis most commonly occurs as part of the complex coagulopathy known as disseminated intravascular coagulation (DIC).
- Microvascular hemostatic derangements occur in association with inflammatory injuries of many types.
- Microvascular thrombosis associated with sepsis is complex and involves increased prothrombotic and antifibrinolytic activity in association with decreased antithrombotic activity.
- Diagnosis and management of DIC are controversial. No consensus exists on how to diagnose and manage this complex disorder.

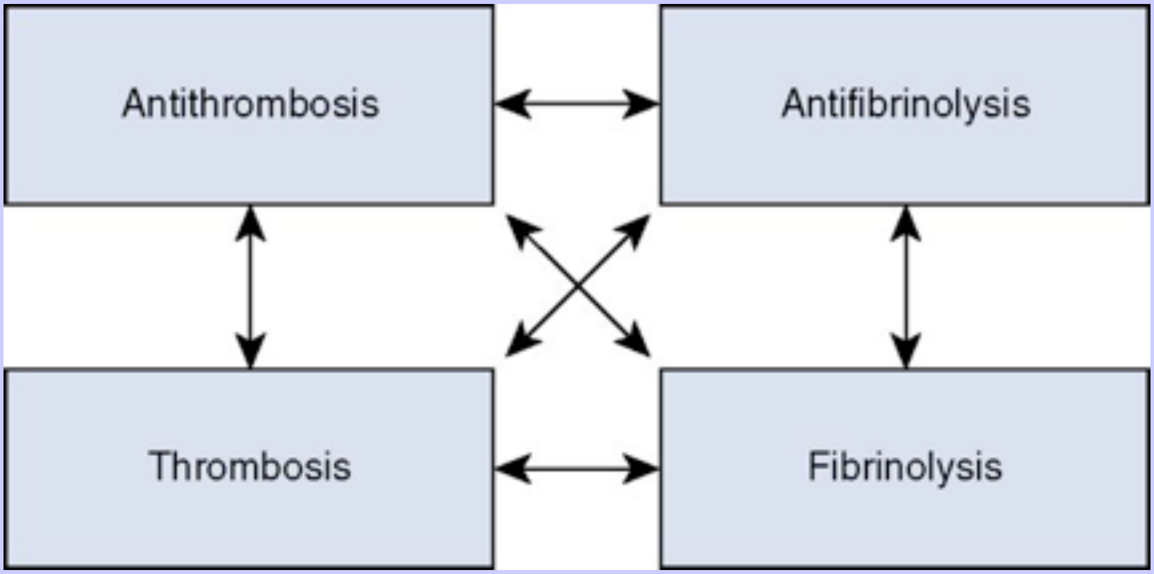
117.3 INTRODUCTION

Our understanding of the complexity of hemostasis has exploded with new information over the past 10 years. Concurrent with the development of molecular biology, and thus our ability to understand molecular interaction on a far more detailed level, there has been a significant improvement in our understanding of sepsis and the innate and acquired immune systems. For the past decade, the study of inflammation, innate immunity, and sepsis has repeatedly intersected with the hemostatic system. As a result, the study of hemostasis has advanced more rapidly than it might have. Over time, the links between these two protective cascades have become undeniably entwined. Several leading thinkers in this field have even postulated that hemostasis and inflammation have evolved together and are not really separate at all, but may be thought of as one incredibly complex defense system.[1-3]

A direct consequence of this work has been a richer and more extensive understanding of hypercoagulable states. Much work remains in order to answer many additional questions; however, many new diagnostic tests and pharmaceutical agents have been studied, and many more will find a place in the diagnosis and management of hypercoagulable states. Traditional approaches to many clinical syndromes are being challenged as new information comes to light. Although many human patients will benefit from this information revolution, there are several challenges for veterinary critical care. It will be difficult to translate results from animal models, human clinical trials, and limited veterinary clinical trials into new clinical practices for our patients. In addition, the costs associated with new diagnostic evaluations and therapies may be prohibitively expensive for many of our clients.

The most common hypercoagulable states that challenge veterinary intensivists daily are of two varieties: microvascular and macrovascular thrombosis. Microvascular thrombosis occurs almost exclusively as the complex coagulopathy associated with the systemic inflammatory response syndrome (SIRS) and sepsis (frequently called *disseminated intravascular coagulation [DIC]*). The most common forms of macrovascular thrombosis in small animal veterinary patients are feline aortic thromboembolism (FATE), and pulmonary thromboembolism. It is important to remember that this field is changing rapidly and that the information contained in this chapter was current at the time of writing, but may change as new insights are gained.

Figure 117-1 Hemostasis model with four interdependent quadrants of function.



117.4 HEMOSTASIS OVERVIEW

Hemostasis is a remarkable interaction of numerous plasma proteins and cells with the singular purpose of forming a seal over damage in the intravascular space and dissolving the patch once vascular healing has taken place. The complexity of these interactions is significant, with countless possible interactions, positive and negative feedback loops among hosts of contributing factors. A modern view of hemostatic function partitions these interactions into a four-quadrant system, with interactions possible among all four major hemostatic forces (Figure 117-1). The purpose of each quadrant is unique. Thrombosis factors work in concert to cause the formation of a platelet-fibrin meshwork seal of the vessel injury. The goal of antithrombotic forces is to limit the development of thrombus or clot in the area of injury and to maintain normal blood fluidity through the remainder of the uninjured vascular space (local control). Fibrinolytic forces will gradually destroy or break down the clot when vessel repair is complete, to allow recanalization of the vessel and return of blood flow. Loss of local control of fibrinolysis would ultimately lead to an inability to form a clot anywhere, so antifibrinolytic factors serve to isolate fibrinolysis to the area of injury or thrombus and maintain local control. In addition, antifibrinolytic factors help protect the clot from fibrinolysis while vessel repair is ongoing. Each quadrant in this system has several important individual molecules (both hemostatic and inflammatory), which interact with the relevant cells involved to achieve their underlying purposes.

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117.5 MACROVASCULAR THROMBOSIS

The pathophysiology of macrovascular thrombosis is best described using Virchow's triad. Virchow postulated that three factors are required for thrombus formation: blood stasis, endothelial injury or pathology, and a hypercoagulable state.[4] This theory remains the foundation of our understanding of thrombosis to date. Blood stasis may occur as a result of abnormal vascular anatomy, such as a dilated left atrium in FATE, or could be subsequent to immobility and low flow states that can occur during surgical procedures, ischemic injury, or critical illness. Causes of endothelial pathology include vascular abnormalities, cardiac jet lesions, and direct vascular trauma. Hypercoagulable states can be acquired, such as occurs with renal loss of antithrombin (AT), or subsequent to hyperadrenocorticism, which leads to increased levels of factors V, X, and fibrinogen.[5] Hypercoagulability may also be congenital. In human medicine, numerous inherited hypercoagulable states have been identified, but as yet these have not been investigated in our veterinary patients.

As previously mentioned, the most common forms of macrovascular thrombosis in small animal veterinary patients are FATE and pulmonary thromboembolism. Pulmonary thromboembolism is discussed further in Chapter 27, Pulmonary Thromboembolism. The clinical signs of macrovascular thrombosis will depend on the anatomic location of the thrombus. Thrombi often are formed in one location and then travel down the vascular system to lodge in a distant location (thromboembolism), where they cause injury via ischemia and associated organ dysfunction. Treatment of macrovascular thrombosis includes administration of anticoagulant drugs, management of underlying disease processes, and possibly thrombolysis. Anticoagulants such as heparin or aspirin are given in an effort to prevent any progression of the thrombus or new thrombus formation (see Chapter 187, Anticoagulants). Treatment of any predisposing underlying disease is very important to prevent further thrombus formation. Administration of thrombolytic drugs aims to cause complete dissolution of the clot and subsequent resolution of the signs. Thrombolytic therapy is not universally successful, can be associated with life-threatening hemorrhage, and when successful may cause life-threatening hyperkalemia as a consequence of postischemia syndrome. Chapter 188, Thrombolytic Agents, discusses thrombolytic therapy in more detail.

117.6 MICROVASCULAR THROMBOSIS

117.6.1 Coagulopathy of Systemic Inflammation

DIC is an umbrella diagnosis that has been used in the past to describe a number of paradoxical thrombohemorrhagic disorders of humans. An international consensus defined DIC as “an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction.”[6] A similar syndrome is present in many veterinary species, and the term *DIC* was also adopted for use in veterinary patients. Numerous conditions have been associated with DIC in veterinary patients (Box 117-1), but the pathophysiology is best understood for the coagulopathy associated with SIRS and sepsis.[7] Arguably, cytokine activation of inflammation or dysregulation of inflammatory signals are the only causes of DIC and are the unifying processes that link all of the disparate causes of DIC.

Several important hemostatic changes occur concurrently during sepsis. Specifically, inflammatory molecular and cellular cross-talk significantly amplifies the raw materials required to stimulate the formation of thrombin and thus stimulate widespread intravascular thrombosis (activated prothrombosis quadrant). In addition, inflammatory molecular and cellular cross-talk damages or inactivates several important antithrombotic cascades (depressed antithrombosis quadrant) that contribute directly to the loss of localization of the hemostatic process. Finally, inflammatory molecular and cellular cross-talk also causes amplification of antifibrinolysis, which protects forming clots from degradation and contributes to widespread microvascular thrombosis (activated antifibrinolytic quadrant). In a patient, the concurrent ischemia and microvascular dysfunction created by the widespread inflammatory cross-talk and intravascular microthrombosis are thought to be significant contributing 503 504 factors in the multiple organ dysfunction that occur with SIRS and sepsis.[8,9]

Microvascular thrombosis occurs when inflammatory cytokines induce expression of tissue factor (TF) on endothelial cells, macrophages, microparticles (liberated from activated monocytes), or exposure of subendothelial TF stores when endothelial cells are damaged. TF expression appears to be mediated predominantly by the inflammatory cytokine interleukin (IL)-6 and triggers explosive fibrin formation through the progressive and complex interactions involving most of the classic numbered clotting factors.[2,10] Platelets are also activated by several inflammatory cytokines and bind to either adhesion glycoproteins on activated endothelial cells or stimulatory ligands in the subendothelial space. Platelet aggregation provides a scaffold for the forming thrombus, and platelet membrane phospholipids are the required site where numerous cooperative assembly proteins gather to produce fibrin. When cross-linking of the fibrin-platelet meshwork is complete, the thrombus is stable and has protected the perceived endothelial damage.

During normal hemostasis, AT exerts its most significant antithrombotic effects by inactivation of factor IIa (thrombin) and factor Xa, which are both crucial to fibrin formation. Antithrombotic activity is dramatically increased locally when the heparin binding site of AT is bound to heparan sulfate proteoglycans (HSPG) present on injured endothelial cells. When bound to endothelial HSPG, AT stimulates the release of prostacyclin I_2 and reduces intracellular nuclear factor kappa-B (NF-κβ) signaling, which both exert potent antiinflammatory effects.[11] Further, when AT binds to syndecan-4 (another HSPG on neutrophils), neutrophil adherence to endothelial cells is inhibited, possibly providing protection from neutrophil inflammatory injury.[12] Thus AT has important antithrombotic and antiinflammatory activity. During systemic inflammatory states, AT activity is decreased, thus allowing thrombosis and inflammation to escalate unopposed. The decrease in AT activity occurs because of decreased production from the liver (AT is a negative acute phase protein), degradation from neutrophil elastase and, most importantly, rapid consumption due to high levels of thrombotic activity.[2,3] In addition, during inflammatory states, enzymatic degradation of HSPG molecules also occurs, further depressing AT activity.

The impact of systemic inflammatory states on the protein C (PC) pathway is also of importance. Thrombomodulin (TM) is an endothelial membrane receptor that has several binding sites. One portion of the TM molecule has intrinsic antiinflammatory properties and down-regulates the NF-κβ and mitogen-activated protein kinase pathways (both are intracellular inflammatory signaling pathways).[13] TM also has a binding site for thrombin that is rapidly inactivated by TM. The thrombin-TM complex then activates PC into activated protein C (APC). The activation of PC occurs much more rapidly when the endothelial protein C receptor (EPCR) binds PC and presents it to the thrombin-TM complex for activation.

Once activated, APC can remain bound to the EPCR, translocate to the endothelial cell nucleus where it inhibits intracellular inflammatory and apoptotic signaling pathways, or it may be released from the EPCR, bind to protein S, and then the APC–protein S complex may exert an antithrombotic effect by inactivating factors Va and VIIIa.[2,3,13] Free APC can also potently decrease leukocyte-endothelial cell adhesion interactions and decrease cytokine production from leukocytes.[14]

The thrombin-TM complex also activates thrombin-activatable fibrinolysis inhibitor (TAFI), which has several important functions. It may cleave residues from the forming clot, making it more resistant to plasmin degradation (antifibrinolytic action). In addition, TAFI is an important inhibitor of C5a, which possesses potent vasoactive effects and may contribute to microvascular dysfunction and the pathogenesis of septic shock.[13] Thus the PC pathway possesses potent antithrombotic, antiinflammatory, antiapoptotic, and positive vasoactive properties. During systemic inflammatory states, several factors contribute to the loss of these functions. Inflammatory cytokines can down-regulate TM and EPCR expression on the endothelial cell surface, decreasing APC activity. Leukocyte activation can damage the PC pathway by releasing oxidizing agents and harmful enzymes. TM is susceptible to oxidative injury from activated neutrophils. In addition, TM can be cleaved from the endothelium by neutrophil elastase, and EPCR by metalloproteinase, and then circulate as soluble forms.[13] Although soluble TM can still activate PC, the efficiency is markedly reduced because of the lack of EPCR contributions to the activation complex. The loss of TM and EPCR from the cell surface permits escalation of intracellular inflammatory and apoptotic signaling. Loss of TM from the endothelial cell surface also decreases TAFI production, which may have a negative impact on vascular function and tissue perfusion.

A third antithrombotic pathway, the TF pathway inhibitor (TFPI) pathway, functions primarily during the early phases of thrombotic activation as the physiologic inhibitor of coagulation factor activation. TFPI is crucial for inhibiting both factor Xa and the primary initiation complex of factor VIIa-TF. Several forms of TFPI are present, and it has a complex trafficking and storage system. The physiologic effects of TFPI are not yet completely understood. Its antiinflammatory function has not been completely characterized.[15]

The function of plasminogen activating inhibitor-1 (PAI-1) is very complex. Subendothelial vitronectin and thrombin are important cofactors for PAI-1 activity. Consequently, PAI-1 activity is most powerful when endothelial damage has occurred and exposed the subendothelial matrix. Platelet α-granules are one of the most important physiologic sources of PAI-1. Thus the predominant physiologic role of PAI-1 is to protect platelet-rich arterial thrombi.[16] It achieves this protective effect by inhibiting plasminogen activators (both tissue type and urokinase type) and thus having an antifibrinolytic effect. In addition, PAI-1–vitronectin complex actively competes for thrombin with TM. As a result, if more thrombin is inactivated by PAI-1–vitronectin, it cannot form a complex with TM, and thus PC activation is strongly inhibited and PAI-1 exerts a prothrombotic effect.[16,17]

Ironically, APC can also inhibit PAI-1. When APC activity is high, PAI-1 function is inhibited, permitting an increase in fibrinolysis in addition to the antithrombotic effects of APC.[16] The net result of these complex interactions between APC and PAI-1 then depends on the relative activity of each factor. The inflammatory cytokines tumor necrosis factor-α (TNF-α), IL-1, and IL-6 stimulate endothelial cells to produce large quantities of PAI-1.[17] This explosive increase in PAI-1, particularly when it complexes with subendothelial vitronectin, has a powerful antifibrinolytic effect. When depletion of APC, from the mechanisms previously discussed, occurs with increased PAI-1 activity, the balance shifts again to further inhibition of APC by PAI-1. The overall effect is enhanced antifibrinolysis and further depression of antithrombotic activity, thus permitting widespread microvascular thrombosis to occur.[16,17]

DIC is a dynamic disease process. In the early stages of hemostatic dysfunction that occur with the inflammatory 504

505 signals outlined above, significant microvascular thrombosis occurs, creating ischemia, further endothelial injury, microvascular dysfunction, and organ dysfunction or failure. As the condition progresses, consumption of important regulatory factors and platelets lead to severe hemostatic dysfunction and hemorrhagic tendencies. Documentation of hypocoagulable states are associated with high mortality of veterinary patients diagnosed with DIC.[18]

117.6.2 Clinical Management of Disseminated Intravascular Coagulation

117.6.2.1 Diagnosis

Despite the new knowledge we have gained in understanding the pathophysiology of the coagulopathy associated with SIRS and sepsis, very disappointing progress has been made in the diagnosis and management of this condition in veterinary patients. Many of the latest diagnostic tools have not yet been validated in veterinary patients or are too expensive to consider for use. Similarly, emerging therapies in human medicine have not been widely evaluated in veterinary patients or are prohibitively expensive. Further progress and clinical evaluations are badly needed to improve the level of care that is provided to veterinary critical care patients suffering from these conditions.

The diagnosis of DIC is not uniformly agreed upon. The lack of an agreed on gold standard test, which new assays or strategies can be compared against, does not allow easy comparison of widely diverging strategies.[19-25] Detection of multiple abnormalities in an appropriate coagulogram will likely continue to form the basis of diagnosis for the foreseeable future. Because recognition of a hypercoagulable state remains challenging, if not impossible, in clinical veterinary medicine, the diagnosis of DIC is largely restricted to identification of the late coagulopathic phase of the disease. See Box 117-2 for a list of common laboratory abnormalities associated with DIC in veterinary patients. Thromboelastography and resonance thromboelastography are promising new diagnostic technologies that evaluate many aspects of the complex coagulopathy with one assay.[26-30] Generalizations about the usefulness of individual assays or diagnostic strategies have yet to be formulated because of the marked diversity of the types of cases studied (both etiologic cause and severity of illness), as well as the small number of cases reported in the literature. It will be important for future studies of DIC in dogs to address these important issues. The development of a consensus strategy for diagnosis of DIC in dogs should remain an important goal of all future research in this area.

117.6.2.1.1

Box 117-2 Laboratory Changes Commonly Associated With the Diagnosis of DIC*

- Thrombocytopenia
- Prolonged prothrombin time
- Prolonged activated partial thromboplastin time
- Hypofibrinogenemia or hyperfibrinogenemia
- Low antithrombin levels
- Positive fibrin degradation products or D-dimers

DIC, Disseminated intravascular coagulation.

* Note these changes are only suggestive of DIC when found in a patient with a proinflammatory disease process such as SIRS and sepsis known to be a cause of DIC.

117.6.2.2

Therapy

The traditional approach to DIC therapy has been (1) the administration of clotting factors in the form of blood component therapy to replenish depleted levels of many important hemostatic factors (2) combined with the administration of anticoagulant drugs, most commonly heparin. At one time, administration of fresh clotting factors and, more importantly, antithrombotic proteins such as AT and PC was thought to bolster the sagging antithrombotic quadrant. It has been through the study of administering highly concentrated forms of specific mediators that we have begun to understand the magnitude of supplementation that is required to achieve changes in outcome or mortality. Supplementation with quantities of specific mediators must be orders of magnitude larger than those contained in component blood products to achieve a measurable change in mortality. For example, AT supplementation must be sufficient to achieve an increase of approximately 1.5 to 2 times the normal activity of AT, in order for a mortality benefit to be seen in animal models and human trials.[31] A study of fresh frozen plasma administration to critically ill canine patients with decreased AT concentrations showed that increases in AT were not documented with moderate doses of fresh frozen plasma.[22] Although few randomized trials have studied the effects of administration of plasma products on mediator concentrations in critically ill patients, even massive doses of fresh frozen plasma did not increase the AT concentration of humans with acute pancreatitis.[32] Based on the evidence, it appears that supplementation with fresh frozen plasma products may be beneficial to patients with DIC syndromes characterized by a hemorrhagic coagulopathy, but for patients who do not have a bleeding tendency, administration of fresh frozen plasma is expensive and does not appear to prevent mortality. Thus, although there appears to be no harm in administering plasma to our patients, it is imperative that we engage clients in a cost-to-benefit discussion before recommending or administering plasma to patients that do not have a bleeding tendency.

Several large trials have been completed in septic humans evaluating the efficacy of concentrated forms of AT, APC, and TFPI.[31,33,34] Only APC has been shown to impart a survival benefit in patients with severe sepsis. Considerable debate has occurred following completion of these trials about factors that may have influenced the results.[35] Further large randomized studies in humans will likely take place in the future to clarify the role of these therapeutic agents in sepsis. Their use has not been documented in veterinary patients.

The second tenet of traditional DIC therapy has been the administration of an anticoagulant drug such as heparin. During the past 5 years, the results of important clinical trials, in addition to extensive research focused on understanding the molecular interactions of inflammation, hemostasis, and the endothelium, have produced sufficient evidence to generate reasonable doubt about the role of heparin in DIC. As mentioned previously, AT possesses numerous important antiinflammatory properties in addition to its antithrombotic actions. Abrogation of all of these beneficial antiinflammatory effects occurs when exogenous heparin is administered.[12,36-38] It is clear that although exogenous heparin may provide an important and significant antithrombotic effect, binding of exogenous heparin to AT prevents binding of the AT molecule to the HSPG on the endothelial surface. Without this endothelial cell surface binding of AT, the important antiinflammatory actions of AT are lost, which may have profound effects when severe inflammatory disease is present.

A retrospective study of canine patients with immune-mediated hemolytic anemia showed that heparin use does not impart a survival benefit in the dogs studied, adding further support to the concept that heparin use in inflammatory disease may be contraindicated.[39] As mentioned previously, heparin therapy has never been subjected to a randomized blinded trial of any significant magnitude to determine if there is a therapeutic effect in patients with DIC. When all the available evidence is considered, however, most of the highest quality evidence suggests that heparin should not be administered to patients with DIC in whom inflammatory diseases exist concurrently. There is overwhelming evidence that heparins have an excellent prophylactic effect in patients at high risk for macrovascular thromboembolism, and their use in such patients who otherwise do not have significant inflammatory disease should not be questioned.[40,41]

117.7 CONCLUSION

The debate over the rightful place of heparin therapy will be active and vigorous in the years to come. The pendulum may swing substantially before settling on a consensus viewpoint. In the meantime, or until further evidence suggests practices to the contrary, heparin should be used with extreme caution in both human and veterinary patients with dysfunctional interactions between the inflammatory and hemostatic systems and the endothelium. The continued use of heparin in patients with minimal inflammatory disease but high risk of venous thromboembolism is justified. What therapy should be administered to patients who exist in the continuum between these two end points is open to debate.

117.8 SUGGESTED FURTHER READING*

SM Donahue, CM Otto: Thromboelastography: a tool for measuring hypercoagulability, hypocoagulability, and fibrinolysis. *J Vet Emerg Crit Care*. **15**, 2005, 9, *An excellent review article outlining the theoretical basis and utility of thromboelastography*.

RD Rosenberg, WC Aird: Vascular-bed-specific hemostasis and hypercoagulable states. *New Engl J Med*. **340**, 1999, 1555, *A human medicine review article providing an excellent overview of the mechanisms of thrombosis*.

E Rozanski, D Hughes, M Scotti, et al.: The effect of heparin and fresh frozen plasma on plasma antithrombin III activity, prothrombin time and activated partial thromboplastin time in critically ill dogs. *J Vet Emerg Crit Care*. **11**, 2001, 15, *Retrospective veterinary study evaluating effectiveness of fresh frozen plasma and heparin on AT levels and patients with preexisting coagulopathy suspected of having DIC*.

A Veldman, D Fischer: The search for a unified theory of coagulation and inflammation. *Cell Mol Life Sci*. **61**, 2004, 2744, *Interesting synthesis of observations offering unique philosophic viewpoint of hemostasis and inflammation*.

S Zeerleder, CE Hack, WA Wuillemin: Disseminated intravascular coagulation in sepsis. *Chest*. **128**, 2005, 2864, *Well-written review article outlining the hemostatic dysfunction associated with sepsis and how the results of three trials of antithrombotic proteins should be interpreted*.

* See the CD-ROM for a complete list of references

118 Chapter 118 Bleeding Disorders

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118.1 KEY POINTS

- Bleeding disorders should always be considered life threatening, necessitating a rapid and efficient diagnostic approach.
- The first diagnostic step is to determine whether bleeding is due to local factors or to a systemic bleeding disorder.
- Bleeding disorders are classified as disorders of primary or secondary hemostasis. Differentiation is usually possible from the physical examination and is vital to establish a diagnosis and make therapeutic decisions.
- Screening laboratory coagulation studies confirm the presence of a bleeding disorder and further characterize the defect.

118.2 INTRODUCTION

Bleeding disorders should always be considered life threatening. Even the stable patient with a bleeding disorder can decompensate rapidly from massive bleeding or bleeding into a vital organ or body cavity. A rapid diagnosis is paramount, so that rational therapy can be instituted with minimal delay. Bleeding disorders are classified as disorders of primary or secondary hemostasis. Differentiation is an essential step in the diagnostic workup.

118.3 PHYSIOLOGY OF HEMOSTASIS

The hemostatic system is complex; the numerous components function as an interrelated continuum to prevent excessive bleeding or thrombosis following injury. For the emergency clinician, however, it is convenient and sufficiently accurate to divide hemostasis into three component parts: primary hemostasis, secondary hemostasis, and fibrinolysis.

Primary hemostasis involves interactions between the platelets and the endothelium, culminating in the formation of the primary hemostatic plug, which constitutes a temporary seal over the injured vessel. At the site of vascular injury, platelets adhere to subendothelial collagen, mediated largely by von Willebrand factor (vWF) and membrane glycoproteins.[1,2] Following adherence, the platelets undergo conformational changes and activation. This includes the release of bioactive agonists that stimulate platelet aggregation and recruitment.[1,2] Aggregated platelets constitute the primary hemostatic plug and provide a stimulus and framework for secondary hemostasis. Defects in primary hemostasis may be due to disorders of the platelets or the vasculature. Platelet disorders can be quantitative (thrombocytopenia) or qualitative (thrombopathia). Vasculopathies result in excessive fragility or abnormal endothelium-platelet interactions.

Secondary hemostasis comprises a series of enzymatic reactions, culminating in the cleavage of plasma fibrinogen to form fibrin, which stabilizes the primary hemostatic plug.[1,3] All coagulation factors participating in secondary hemostasis are produced in the liver. Factors II (thrombin), VII, IX, and X are proenzymes that undergo a vitamin K–dependent modification before secretion from hepatocytes.[1,3] Classically, two pathways of coagulation activation are recognized: an intrinsic and an extrinsic pathway (Figure 118-1). The intrinsic pathway is surface activated and operates strictly with the components present in the blood, whereas the extrinsic pathway requires a tissue factor for activation. These two pathways converge in a final common pathway of thrombin generation and fibrin formation. Defects of secondary hemostasis may be quantitative or qualitative coagulation factor disorders, or both.

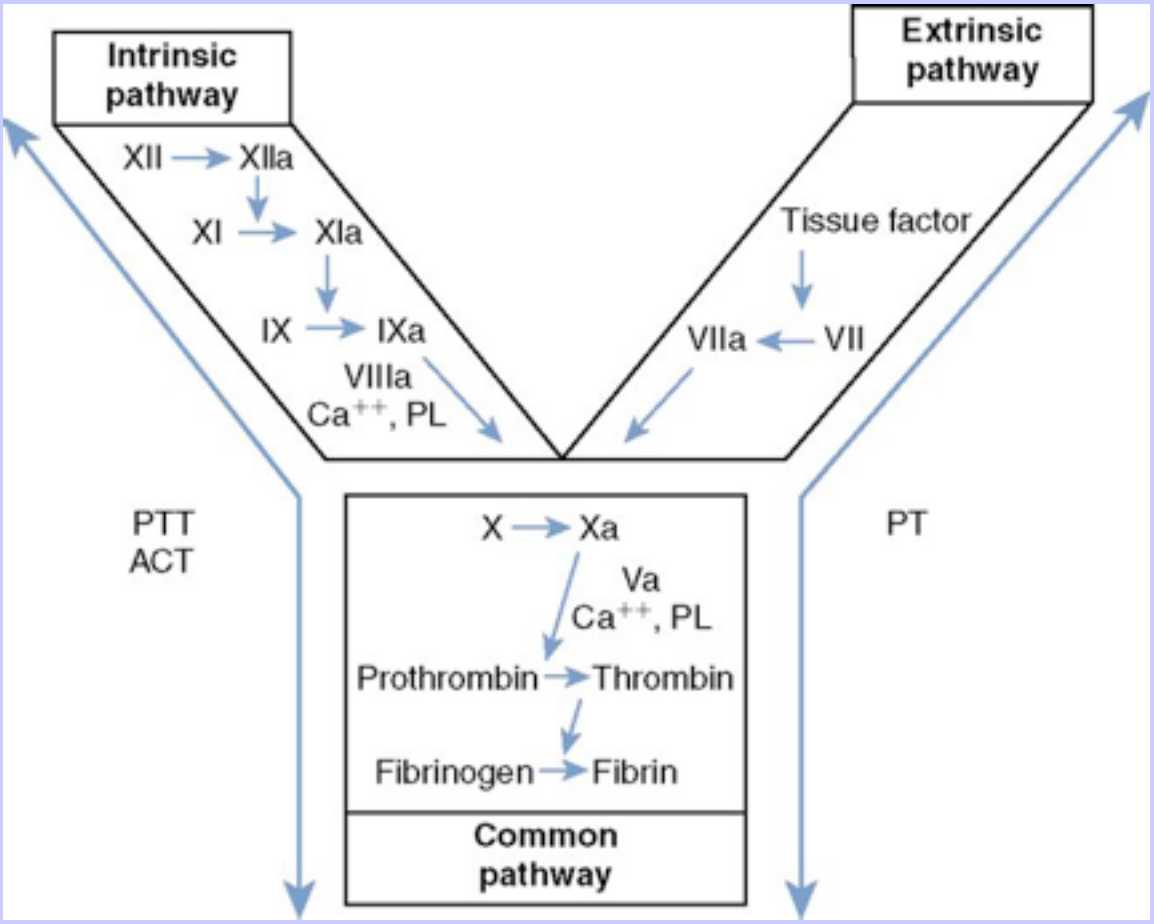
The fibrinolytic system consists of plasminogen and all substances that convert it to its active form, plasmin. Plasmin is responsible for dissolution of the fibrin clot. Dissolution results in the production of various fragments called *fibrin split products (FSPs),* also known as *fibrin degradation products*. FSPs ultimately are removed from the circulation by the liver (half-life approximately 9 to 12 hours).[4] FSPs interfere with platelet function and inhibit thrombin, thus contributing to a bleeding tendency.[1,4] The breakdown of fibrinogen can also increase measured levels of FSPs or FDPs.

118.4 EMERGENCY APPROACH TO THE BLEEDING PATIENT

The patient may present for bleeding that is evident to the owner. It may also present for signs related to anemia from ongoing hemorrhage, or signs due to acute bleeding that compromises organ function or hemodynamics. Patients in an anemic crisis are depressed or moribund, with marked pallor, tachypnea, tachycardia, and bounding pulses. If bleeding has been gradual and there has been sufficient time for compensatory fluid shifts, the patient may be weak but hemodynamically stable. If anemia is due to substantial acute blood loss, signs of hypoperfusion predominate. Hemorrhage into the brain, spinal cord, myocardium, or lungs can result in acute organ compromise without significant anemia or shock.

A primary survey should be performed in any emergency patient. This is the initial rapid assessment of vital organ systems to determine if a life-threatening situation exists. Hypovolemic shock, an anemic crisis, and pulmonary or brain hemorrhage constitute life-threatening situations in the bleeding patient. Venous access should be established without delay and blood collected from the catheter for a minimum database, including a packed cell volume (PCV) and total protein (TP). In the bleeding animal, both PCV and TP are usually decreased. In animals with 507 acute hemorrhage, however, the PCV may be normal or elevated as a result of inadequate time for fluid 508 redistribution or compensatory splenic contraction. A low TP in a hypovolemic patient is suggestive of acute blood loss, regardless of the PCV. Additional blood samples should be collected before initiating therapy to avoid treatment-induced changes in laboratory parameters. These should include a blood smear, serum, ethylenediaminetetraacetic acid (EDTA) plasma sample, and citrated plasma sample for later testing.

Figure 118-1 Schematic representation of secondary hemostasis, indicating the factors evaluated by the screening coagulation tests. *ACT,* Activated clotting time; *PL,* platelet phospholipid; *PTT,* partial thromboplastin time; *PT,* prothrombin time.



Following sample collection, therapy should be initiated to stabilize the patient. Initial stabilization of the bleeding patient involves (1) control of hemorrhage, when possible; (2) blood transfusion, if anemia is significant; and/or (3) blood volume replacement, when hypoperfusion is present (see Chapters 65 and 66, Shock Fluids and Fluid Challenge and Transfusion Medicine, respectively). In animals with hemorrhagic shock, the most life-threatening problem is hypoperfusion. Initial therapy therefore should involve aggressive fluid therapy (isotonic crystalloids with or without synthetic colloid fluids) until blood is available. There is no justification for withholding fluid therapy in the anemic patient. Hypoperfusion will only exacerbate the tissue hypoxia.

The patient with a suspected hemorrhagic tendency should be kept quiet. Subcutaneous injections should be avoided, when possible, and venipuncture performed only when required for platelet enumeration. Venipuncture sites should be held with manual pressure for atleast 5 minutes. An intravenous catheter usually can be placed safely and is used to collect all other blood samples. The patient should be monitored closely for evidence of ongoing or recurrent hemorrhage, including evaluation of perfusion, respiratory, and neurologic status, mucous membrane color, and PCV and TP, as well as monitoring of blood pressure and electrocardiogram. Following initial stabilization, every effort should be directed toward establishing a rapid diagnosis.

118.5 DIAGNOSTIC APPROACH

Three initial questions must be answered: (1) Is the bleeding a result of local factors or does the patient have a generalized bleeding disorder? (2) If a systemic bleeding disorder does exist, what is the nature of the defect (primary or secondary hemostasis)? (3) Is the defect congenital or acquired? These questions can usually be answered based on the history, physical examination, and screening laboratory tests.

118.5.1 History

The importance of a thorough and detailed history cannot be overemphasized. Information should be sought regarding past or present bleeding episodes that prompted presentation or a history of recent trauma. In some cases, bleeding may not be apparent to the owner. Lameness may result from hemarthrosis and dyspnea from intrapulmonary hemorrhage. The owner should be questioned regarding any evidence of bleeding in other sites that would indicate a systemic bleeding disorder.

The signalment of the patient may be informative. Severe inherited disorders are generally apparent within the first 6 months of life. Milder forms, such as von Willebrand disease (vWD), may not be diagnosed until surgery, trauma, or concurrent disease precipitates bleeding. Acquired hemostatic anomalies are seen more commonly in mature animals. It can be difficult to differentiate between a mild inherited defect and a newly acquired disorder. A history of repeated bleeding episodes suggests a possible inherited coagulopathy. Acquired disorders can occur in any breed. Some breeds, however, appear to be more prone to certain disorders (e.g., immune-mediated thrombocytopenia [IMTP] in Cocker Spaniels). Inherited disorders show a much higher breed predilection.

The clinician should try to determine whether bleeding episodes occurred spontaneously or were precipitated by injury or surgery. Some inherited disorders (e.g., hemophilia) and many acquired disorders (e.g., thrombocytopenia, vitamin K deficiency) produce spontaneous bleeding, whereas milder forms of these diseases and other conditions (e.g., vWD, factor VII deficiency) more commonly require some form of trauma to make the clotting impairment clinically apparent. The assessment of response to trauma may also enable the clinician to date the onset of the disorder. A patient that has tolerated surgery is unlikely to have a severe inherited bleeding disorder.

The history should include detailed enquiries about previous illnesses and past and present medications. Many systemic diseases can compromise hemostasis and precipitate clinical bleeding, particularly in a patient with an already compromised hemostatic mechanism. Numerous drugs have been associated with thrombocytopenia, thrombopathias, and coagulopathies. Live-virus vaccines and certain drugs can cause thrombocytopenia 3 to 10 days post administration. A travel history may elucidate exposure to infectious diseases. Specific enquiries about the environment and patient behavior may reveal the potential of exposure to toxins or trauma.

When possible, information should be sought concerning the animal's family members. Although a family history of bleeding disorders has great diagnostic significance, a negative history does not exclude the possibility of a heritable disorder.

118.5.2 Physical Examination

Evaluation of the distribution and extent of current hemorrhage requires careful examination of all body systems including the skin, mucous membranes, eyes, and joints, as well as the urine and feces. The presence of hemorrhage in more than one site is suggestive of a bleeding disorder. The nature of the hemorrhage helps to characterize the defect. Defects of primary hemostasis are characterized by petechiae or ecchymosis and spontaneous bleeding from mucosal surfaces, including epistaxis, gingival bleeding, hyphema, hematuria, and melena. Platelet and vascular abnormalities cannot be distinguished by physical examination alone. Defects of secondary hemostasis usually are characterized by single or multiple hematomas and bleeding into subcutaneous tissue, body cavities, muscles, or joints. Some acquired disorders, such as disseminated intravascular coagulation (DIC), defy this classification because multiple hemostatic defects are present. vWD usually has the characteristics of a primary hemostatic defect, but in its most severe form it may mimic a secondary hemostatic disorder. 508 509

Table 118-1 Screening Tests for the Evaluation of Hemostasis

Process	Screening Test	Component Evaluated
Primary hemostasis	Platelet enumeration*	Platelet numbers
	Platelet estimation†	Platelet numbers
	Buccal mucosal bleeding time*	Platelet numbers and function, vascular integrity
Secondary hemostasis	Activated clotting time†	Intrinsic and common pathways: factors XII, XI, IX, VIII, X, V, II, and fibrinogen
	Partial thromboplastin time*	As with ACT, but more sensitive
	Prothrombin time*	Extrinsic and common pathways: factors III, VII, X, V, II, and fibrinogen
Fibrinolysis	Fibrin split products*	Products of fibrinolysis or fibrogenolysis
	D-Dimers*	Products of fibrinolysis; specific for lysis of cross-linked fibrin

ACT, Activated clotting time.

Many systemic diseases have the potential to impair hemostasis and result in bleeding, or to precipitate bleeding in an animal with already compromised hemostasis. It is important that a thorough examination be aimed at identifying such diseases. Hepatic failure can produce a variety of hemostatic defects. Thrombopathias have been associated with renal disease and neoplasia. Some forms of neoplasia can result in IMTP or DIC. Examination should also evaluate for evidence of other immune-mediated disease (e.g., cutaneous or mucocutaneous lesions, arthropathy, chorioretinitis).

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[*] In-office assays available.

[†] In-office tests.

118.5.3 Screening Laboratory Tests

Laboratory tests are essential to confirm and characterize the hemostatic defect (Table 118-1). These tests should be performed and interpreted carefully, along with the clinical findings, and with their individual limitations in mind. Normal values are listed in Table 118-2.

118.5.3.1 Sample Collection

Blood samples should be collected before initiation of any therapy. Hemostatic tests usually require specific sampling techniques. Improper technique or use of an incorrect container or handling methods results in activation of coagulation and false results. For platelet enumeration, EDTA is required. Most of the tests for secondary hemostasis, the individual coagulation factors, and D-dimers are measured from citrated blood or plasma. Prefabricated sample containers are generally used. Citrated tubes contain sufficient volume of citrate solution such that the ratio of citrate to blood is 1:9. Should there be deviations of this ratio, incorrect test results are obtained. This ratio, however, is valid for animals with a physiologic hematocrit. It can be adjusted via controlled underfilling for patients with a decreased hematocrit or controlled overfilling for those with an increased hematocrit.[5]

Blood collection should be performed without, or after brief (<30 seconds), venous congestion. Venipuncture should be quick and atraumatic. Puncture of the same vein should not be repeated within 30 minutes.[5] Use of the Vacutainer system is not generally recommended. Aspiration with a syringe and sample transfer into the tube should be performed carefully. Rapid and thorough mixing of the collected blood with the anticoagulant should be performed using careful inversion and rotation.

118.5.3.2 Platelet Enumeration and Estimation

Quantitative platelet disorders are detected via a platelet count. This should be performed in all patients with a suspected bleeding disorder. Samples are collected in EDTA and analyzed either manually (by hemocytometer) or with an automated cell counter. Both techniques are reliable for canine blood. In cats, there is considerable overlap between erythrocyte and platelet volumes, resulting in erroneous platelet results from automated counters.[6] For this reason, feline platelets should be enumerated manually.

Examination of a blood smear allows for rapid estimation of platelet numbers. This is essential in the emergency setting where automated counts may not be available, and in cats, in which automated counts are frequently inaccurate. Smear examination also serves to verify the findings of automated counters. Because platelet clumping can result in artifactually low counts, a decreased platelet count should always be verified via smear evaluation and, if necessary, the count repeated on a freshly drawn blood sample. On a well-distributed smear, an average of 11 to 25 platelets per high-power field is considered normal.[7] Each platelet in such a field represents a count of approximately 15,000/µl. Large platelets (macroplatelets or “shift” platelets) generally indicate megakaryocytic hyperplasia and a regenerative response. The blood smear should also be examined for schizocytes (fragmented erythrocytes), which suggest microangiopathic hemolysis (e.g., DIC).

118.5.3.3 Bleeding Time

The bleeding time is the duration of hemorrhage resulting from infliction of a small standardized injury involving only microscopic vessels. The buccal mucosal bleeding time (BMBT) is the most reliable and reproducible method.[8] Normal values can be found in Table 118-2. Cats usually require light sedation for a BMBT. The patient is restrained in lateral recumbency and a strip of gauze is tied around the maxilla to fold up the upper lip, tightly enough to cause moderate mucosal engorgement. A two-blade, spring-loaded device (Simplate II, Organon Teknika Corporation, Jessup, MD) is used to make two 1-mm deep incisions in the mucosa of the upper lip. The incisions should be made at a site devoid of visible vessels and inclined so that the blood flows toward the mouth. Shed blood is blotted carefully with filter paper, taking extreme care not to disturb the incisions. The BMBT is the time from creation of the incision to cessation of bleeding.

Table 118-2 Normal Values for Screening Laboratory Tests of Hemostasis

Test	Dog	Cat
Platelet count (× 10^3/µl)	200 to 500	200 to 600
Buccal mucosal bleeding time (minutes)	1.7 to 4.2	1.4 to 2.4
Cuticle bleeding time (minutes)	2 to 8	2 to 8
Activated clotting time (seconds)	60 to 110	50 to 75
Prothrombin time (seconds)	6 to 11	6 to 12
Partial thromboplastin time (seconds)*	10 to 25	10 to 25
Fibrin split products (µg/ml)*	<10	<10
D-Dimers (latex agglutination) (ng/dl)	<250	<250

The cuticle bleeding time is the duration of bleeding after the tip of the dermis of the nail has been severed by a guillotine-type nail clipper. It is significantly less reliable and reproducible than the BMBT, and thus cannot be recommended.

The bleeding time reflects in vivo primary hemostasis. It is prolonged in patients with thrombocytopenia, thrombopathia, and/or vascular anomalies. It is indicated in animals with a suspected primary hemostatic defect when the platelet count is adequate. The test is unnecessary in the thrombocytopenic patient.

* Normal values are laboratory and technique dependent. Normal values for patient-side coagulometers are provided by the manufacturer.

118.5.3.4 Activated Clotting Time

The activated clotting time (ACT) is a simple, in-office screening test for the intrinsic and common pathways.[5] Blood (2 ml) is drawn into a prewarmed (37° C) commercial tube containing diatomaceous earth, which serves as a chemical activator of factor XII. The first few drops of blood are discarded because of the possible presence of tissue factor. The sample is mixed by inversion and then placed in a 37° C heat block or water bath for 50 seconds. It is inverted every 10 seconds, observed for clot formation, and replaced. The ACT is the interval to first clot formation. The ACT is not prolonged until a single factor is decreased to below 10% of normal concentration, or multiple defects are present. It is therefore a relatively insensitive, but easily performed, test. Severe thrombocytopenia (<10,000/μl) causes mild prolongation of the ACT (10 to 20 seconds).[9] Similarly, hypofibrinogenemia and some thrombopathias may result in prolonged ACTs.[9]

118.5.3.5

Partial Thromboplastin Time

The partial thromboplastin time (PTT) tests the intrinsic and common pathways (see Figure 118-1). Only factors VII and XIII are not evaluated. In general, at least one factor must be decreased to below 25% to 30% of normal concentration before PTT prolongation occurs.[10] This test is therefore more sensitive than the ACT and is not affected by primary hemostatic disorders.

A patient-side coagulometer (SCA 2000, Synbiotics, San Diego, CA) is an attractive alternative to conventional laboratory PTT determination in the emergency setting. Although the methodology enables testing of either nonanticoagulated blood or citrated whole blood, the latter is preferable to enhance the sensitivity and specificity. Using citrated whole blood, reported sensitivity is 100%, with a specificity of approximately 83%.[11] As such, it is an excellent screening test for defects of the intrinsic and common pathways. False-positive results, however, do occur. A prolonged PTT on the SCA should be validated via conventional laboratory testing. In the author's experience, marked prolongations are usually clinically significant; mild prolongations should be interpreted with caution.

118.5.3.6

Prothrombin Time

The prothrombin time (PT) tests the extrinsic and common pathways (see Figure 118-1). Thus it is the principal test of the extrinsic pathway.[10] Because of the short half-life of factor VII, this test is very sensitive to vitamin K deficiency or antagonism. It is less sensitive to the effects of heparin than is the PTT.

The patient-side coagulometer is also a relatively accurate method for PT testing. Using citrated whole blood, the reported sensitivity and specificity are 85.7% and 95.5%, respectively.[11] That is, some defects of the extrinsic system will not be detected, and false-positive results occur. Abnormal results that do not correlate with clinical findings should be verified via conventional laboratory testing.

118.5.3.7

Fibrin Split Products and Fibrin Degradation Products

FSPs are generated when fibrinogen, soluble fibrin, or cross-linked fibrin is lysed. Commercial latex agglutination kits allow for a rapid, semiquantitative method for FSP determination.[9] Samples are collected with specialized tubes. Elevated concentrations commonly occur in DIC but are not universally present, nor specific for the syndrome. Increased concentrations may also occur in patients with hepatic disease, due to enhanced fibrinolysis and reduced fibrin clearance. False elevations may occur in patients receiving heparin therapy or those with dysfibrinogenemia.

118.5.3.8

D-Dimer

D-dimers are unique FSPs that are formed when cross-linked fibrin is lysed by plasmin. In contrast to FSPs, which indicate only the activation of plasmin, D-dimers indicate the activation of thrombin and plasmin and are specific for active coagulation and fibrinolysis.[12,13] The half-life of D-dimers is short (approximately 5 hours).[13] As such, they are useful only for detection of recent or ongoing fibrinolysis. The traditional laboratory assay of D-dimers is the enzyme-linked immunosorbent assay (ELISA). An in-office latex bead agglutination test (Accuclot D-dimer, Sigma, St. Louis, MO) and a canine-specific point-of-care test (AGEN canine D-dimer test, Sigma) have been shown to compare favorably.

The D-dimer is a sensitive test for DIC and likely is superior to traditional FSP assays for this purpose. However, D-dimer concentrations are not always elevated in patients with DIC, and elevated D-dimer levels are certainly not specific for DIC. Elevated concentrations have been demonstrated in dogs with thromboembolism, neoplasia, hepatic disease, renal failure, cardiac failure, internal hemorrhage, and following surgical procedures.[13] It should be considered an ancillary diagnostic test, with the diagnosis of DIC relying on the appropriate constellation of clinical findings and abnormal hemostatic testing results.

118.5.3.8.1

Box 118-1 Causes of Disorders of Primary Hemostasis

118.5.3.8.1.1

Thrombocytopenia

118.5.3.8.1.1.1

Decreased Production

- Drug-induced disorders (estrogen, chloramphenicol, cytotoxic agents)
- Immune-mediated megakaryocytic hypoplasia
- Viral (FeLV)
- Chronic rickettsial disease
- Estrogen-secreting neoplasm
- Myelophthisis (myeloproliferative disease)
- Myelofibrosis
- Cyclic thrombocytopenia *(Ehrlichia platys)*
- Radiation
- Idiopathic bone marrow aplasia

118.5.3.8.1.1.2

Increased Destruction

- Immune-mediated thrombocytopenia (IMTP)

118.5.3.8.1.1.3

Primary

Idiopathic

Evan syndrome (IMHA and IMTP)

Systemic lupus erythematosus

118.5.3.8.1.1.4

Secondary

Drugs

Live-virus vaccination

Tick-borne disease (e.g., Rocky Mountain spotted fever)

Neoplasia

Bacterial infection

Drug-induced disorders

Ehrlichiosis

Dirofilariasis

118.5.3.8.1.2

Consumption and Sequestration

Disseminated intravascular coagulation

Microangiopathies

Sepsis

Vasculitis

Splenic torsion, hypersplenism

Hepatic disease

Profound, acute hemorrhage

Hemolytic uremic syndrome

118.5.3.8.1.3 Thrombopathia

118.5.3.8.1.3.1 Acquired

Drugs (NSAIDs, β-lactam antibiotics, calcium channel blockers, synthetic colloid solutions)

Uremia

Hepatic disease

Myeloproliferative disorders

Dysproteinemia (myeloma)

Ehrlichiosis

Snake venom

118.5.3.8.1.3.2 Inherited

Von Willebrand disease (many dog breeds, rare in cats)

Canine thrombopathia (Basset Hounds, Spitz dogs)

Thromboasthenic thrombopathia (Otterhounds)

Chédiak-Higashi syndrome (Persian cats)

Storage pool defect (American Cocker Spaniel)

118.5.3.8.1.4 Vascular Disorders

118.5.3.8.1.4.1 Acquired

- Vasculitis
- Hyperadrenocorticism
- Atherosclerosis

118.5.3.8.1.4.2 Inherited

- Ehlers-Danlos syndrome

118.6 DISORDERS OF PRIMARY HEMOSTASIS

The causes of disorders of primary hemostasis are listed in Box 118-1. An algorithmic diagnostic approach is outlined in Figure 118-2.

118.6.1 Thrombocytopenia

Thrombocytopenia is the most common primary hemostatic defect. It can result from decreased platelet production, platelet destruction, consumption, or sequestration. Spontaneous bleeding generally does not occur until platelet counts fall below 20,000/µl to 50,000/µl, unless a concomitant bleeding disorder exists. The bleeding patient with a mild or moderate thrombocytopenia either has a combined defect, or the thrombocytopenia is merely a consequence of acute hemorrhage. Disorders of consumption/sequestration generally result in a mild or moderate degree of thrombocytopenia. Exceptions occur in some cases of splenic torsion and DIC, in which thrombocytopenia can be marked. (When DIC results in severe thrombocytopenia, it is almost invariably accompanied by other abnormal hemostatic test results.)

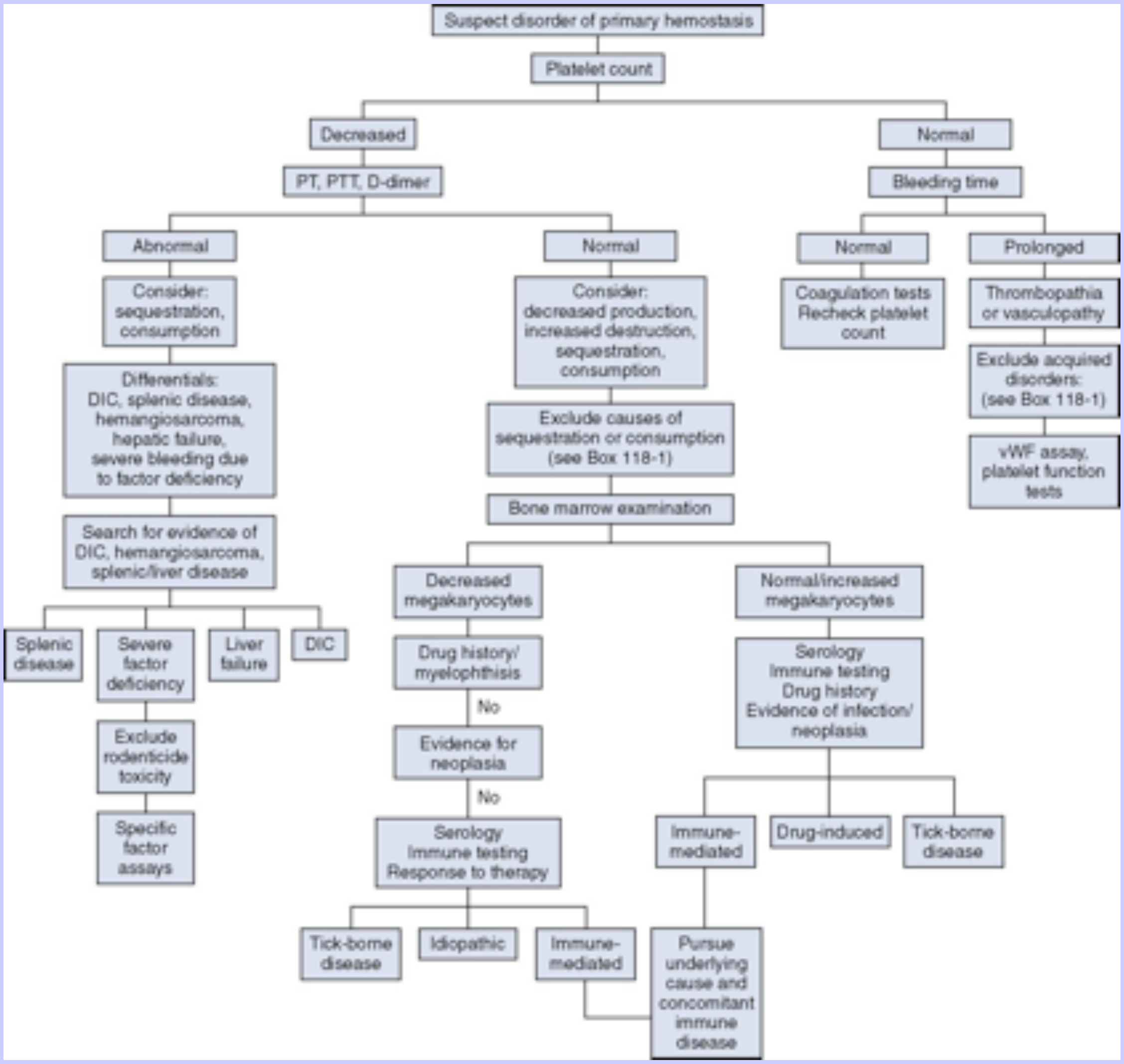
The secondary hemostatic mechanisms should be evaluated in all thrombocytopenic animals to determine the etiology. If these are normal, a bone marrow aspirate or biopsy is indicated to evaluate platelet production. The diagnostic approach to patients with thrombocytopenia and the treatment of such disorders are discussed in detail in Chapter 119, Thrombocytopenia.

118.6.2 Thrombopathia

Vascular disorders are a relatively uncommon cause of bleeding. In the patient with a primary hemostatic disorder and normal platelet numbers, a platelet function defect is likely. A prolonged BMBT in a patient with adequate platelet numbers confirms thrombopathia. The drug history should be carefully appraised, because numerous drugs can cause or contribute to thrombopathia.[14] Diseases known to precipitate platelet dysfunction should be excluded. If no obvious cause of acquired thrombopathia can be found, a hereditary disorder is suspected.

vWD is the most common canine hereditary bleeding disorder. vWF is produced and stored in canine endothelial cells and plays a central role in platelet adhesion.[15] In plasma, vWF forms a complex with coagulation factor VIII and appears to stabilize the functional half-life of this factor. High-molecular-weight vWF multimers are 511 512 most effective in augmenting platelet adhesion. Deficiency of vWF, or preferential loss of high-molecular-weight forms, results in impaired adhesion.

Figure 118-2 Algorithmic approach to disorders of primary hemostasis. *DIC,* Disseminated intravascular coagulation; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *vWF,* von Willebrand factor.


Suspect disorder of primary hemostasis
Platelet count
Decreased
PT, PTT, D-dimer
Abnormal
Consider: sequestration, consumption
Differentials: DIC, splenic disease, hemangiosarcoma, hepatic failure, severe bleeding due to factor deficiency
Search for evidence of DIC, hemangiosarcoma, splenic/liver disease
Splenic disease
Severe factor deficiency
Liver failure
DIC
Exclude rodenticide toxicity
Specific factor assays
Normal
Consider: decreased production, increased destruction, sequestration, consumption
Exclude causes of sequestration or consumption (see Box 118-1)
Bone marrow examination
Decreased megakaryocytes
Drug history/ myelophthisis
No
Evidence for neoplasia
No
Serology Immune testing Response to therapy
Tick-borne disease
Idiopathic
Immune-mediated
Normal/increased megakaryocytes
Serology Immune testing Drug history Evidence of infection/ neoplasia
Immune-mediated
Drug-induced
Tick-borne disease
Pursue underlying cause and concomitant immune disease
Normal
Bleeding time
Normal
Coagulation tests Recheck platelet count
Prolonged
Thrombopathia or vasculopathy
Exclude acquired disorders: (see Box 118-1)
vWF assay, platelet function tests

There are three types of vWD.[15,16] Type I is most common. It is associated with a partial, quantitative deficiency of vWF, with normal multimer distribution. Type I vWD has been described in numerous dog breeds, including the Doberman, Rottweiler, and German Shepherd. Isolated cases have been reported in cats. Clinical severity is variable and correlates with the reduction in vWF concentration. Severely affected dogs (<20% vWF) can bleed spontaneously. Mildly affected dogs will bleed excessively only if subjected to surgery or trauma or if the condition is exacerbated by another bleeding tendency. Type II vWD is characterized by low vWF concentration and a disproportionate loss of high-molecular-weight multimers. It has been described in German Shorthaired Pointers and Wirehaired Pointers. Type III vWD is a severe quantitative deficiency of vWF. Familial forms have been reported in Chesapeake Bay Retrievers, Shetland Sheepdogs, and Scottish Terriers. Sporadic cases have been reported in other breeds. Types II and III vWD cause a severe bleeding tendency, typically with episodes of hemorrhage occurring within the first year of life.

Definitive diagnosis of vWD requires assay of plasma vWF. ELISA is the most widely used test to detect animals with vWD reported as a percentage of the laboratory's standard plasma. Values less than 50% are considered to indicate vWF deficiency. Differentiation between types I and II vWD requires determination of multimer distribution via immunoelectrophoresis. Animals with systemic stress or critical illness may have abnormal vWF. Therefore decreased vWF titers in such patients should not be overinterpreted.

Control of hemorrhage in a dog with vWD includes the administration of plasma transfusions that contain vWF. 512
Cryoprecipitate is the ideal plasma product, because the concentration of vWF is 5 to 10 times that of plasma. 513
Fresh frozen plasma is an acceptable alternative if cryoprecipitate is not available. Cryoprecipitate is administered at a dosage of 1 unit/10 kg (1 unit being the cryoprecipitate yielded from 200 ml plasma), or fresh frozen plasma at 6 to 12 ml/kg.[15] Desmopressin (DDAVP) can also be given to dogs with type I vWD. The drug is believed to act by stimulating release of intracellular vWF stores.[17] Duration of effect, however, can be limited. Because of the costs of injectable DDAVP, the intranasal form generally is used, given at 1 to 4 μg/kg SC.[16] It can be administered during a bleeding crisis, or 30 minutes before surgery. Efficacy is determined by repeating the BMBT 30 to 60 minutes after administration. Close monitoring is required, and appropriate transfusion products should be available if response to DDAVP is inadequate.

118.6.2.1 Box 118-2 Causes of Disorders of Secondary Hemostasis

118.6.2.1.1 Acquired

Vitamin K deficiency and antagonism

Hepatopathy

Disseminated intravascular coagulation

Pharmacologic anticoagulants (e.g., heparin)

118.6.2.1.2 Inherited Factor Deficiencies

I: Hypofibrinogenemia and dysfibrinogenemia (Bernese Mountain Dog, Borzoi, Lhasa Apso, Vizsla, other dog breeds)

II: Hypoprothrombinemia (Boxer, Otterhound, English Cocker Spaniel)

VII: Hypoproconvertinemia (Beagle, Malamute, Boxer, Bulldog, Miniature Schnauzer, mixed breed dogs)

VIII: Hemophilia A (German Shepherd, other dog breeds, mixed breed dogs, cats)

IX: Hemophilia B (numerous dog breeds; cats)

X: Stuart-Prower trait (American Cocker Spaniel, Jack Russell Terrier, mixed breed dogs)

XI: Plasma thromboplastin antecedent deficiency (English Springer Spaniel, Kerry Blue Terrier, Great Pyrenees)

XII: Hageman factor deficiency (Miniature Poodle, Standard Poodle, German Shorthaired Pointer, Shar Pei; cats)

118.7

DISORDERS OF SECONDARY HEMOSTASIS

Box 118-2 lists the causes of disorders of secondary hemostasis (coagulopathies) in small animals. Figure 118-3 outlines an algorithmic diagnostic approach in these patients.

Hereditary coagulopathies are quantitative disorders of specific coagulation factors, usually noted in purebred dogs. Acquired disorders include vitamin K deficiency/antagonism, hepatic disease, DIC, and the presence of anticoagulants (e.g., heparin). These acquired conditions tend to affect multiple factors in both the intrinsic and extrinsic pathways. Factor VII has the shortest half-life (4 to 6 hours), so prolongation of the PT may precede PTT prolongation in early vitamin K deficiency or early acute hepatic failure. Conversely, the PTT alone may be prolonged with chronic hepatic disease, DIC, or heparin therapy, or with fluid administration (e.g., synthetic colloid therapy or massive crystalloid fluid administration).

118.7.1

Anticoagulant Rodenticide Toxicity

The most common cause of vitamin K deficiency in dogs is the ingestion of anticoagulant rodenticides. Synthesis of vitamin K–dependent factors (II, VII, IX, and X) occurs in the liver. Vitamin K is an essential cofactor for carboxylation of these proteins, rendering them functional. Anticoagulant rodenticides interfere with recycling of vitamin K, resulting in rapid depletion.

Clinical signs of a secondary hemostatic disorder generally occur 2 to 3 days post ingestion. Prolongation of the PT occurs first, but, by the time hemorrhage is evident, the PT, PTT, and ACT are usually all prolonged. FSP, D-dimer, and fibrinogen concentrations are generally normal. The platelet count is usually normal, but it may be decreased by consumption during bleeding. Toxicologic testing is not usually helpful in the emergency situation, but it may serve to confirm an uncertain diagnosis. Anticoagulant rodenticide intoxication is discussed in greater detail in Chapter 82, Rodenticides.

118.7.2 Hepatic Disease

Severe hepatocellular damage or biliary obstruction results in variable factor deficiencies and/or abnormalities in vitamin K metabolism.[18] Both quantitative and qualitative platelet disorders may occur. PT and PTT can be prolonged. FSP and D-dimer concentrations may be elevated. Excessive fibrinolysis can result from the reduced clearance of plasminogen activators and reduced synthesis of fibrinolytic inhibitors. Differentiation from DIC is sometimes impossible based on coagulation testing alone and therefore must relay on clinical findings, serum chemistry results, and liver function testing. Bleeding tendencies must be corrected before pursuing hepatic biopsy or other invasive procedures. Transfusion of fresh frozen plasma can temporarily offset factor deficiencies. Vitamin K_1 may be beneficial in some patients; efficacy should be ascertained by repeat coagulation testing at least 12 hours after initiating therapy.

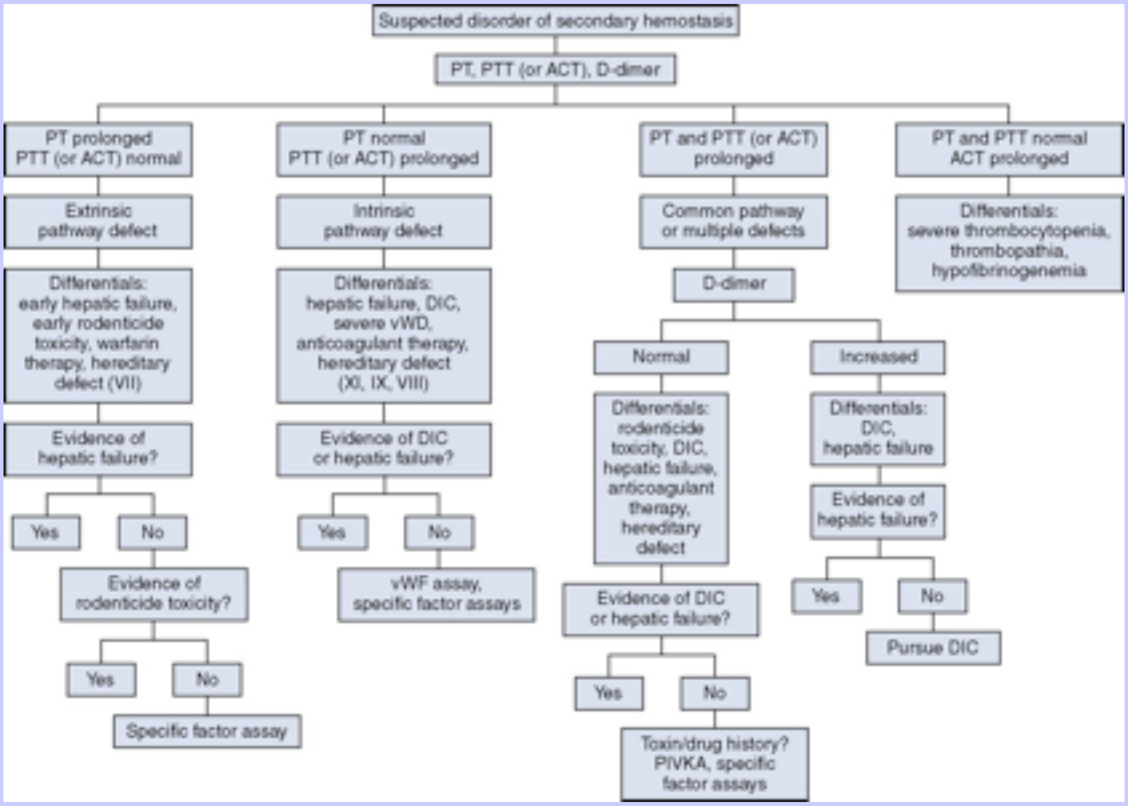
118.7.3 Disseminated Intravascular Coagulation

DIC refers to the intravascular activation of hemostasis with resultant microcirculatory thrombosis. Exaggerated consumption of platelets and coagulation factors results in defective hemostasis and a bleeding tendency. Fibrinolysis of microthrombi generates FSPs, further exacerbating the disorder. The consumption or loss of natural anticoagulants can precipitate a thrombotic tendency.

The diagnosis of acute, fulminant DIC is usually made easily, but diagnosing chronic or subclinical DIC may prove more difficult. There is always an underlying disease causing DIC that should be identified rapidly, if possible. Laboratory findings are extremely variable. Thrombocytopenia is almost invariably present, but relative changes may be undetected unless a recent count is available for comparison. The PT, and more often the PTT, may be prolonged, but both may be normal if compensatory factor production is adequate. Significant elevations of FSP or D-dimer levels are highly suggestive of DIC, but are nonspecific. Schizocytes on blood smear examination are significant, but they are not always present and may occur with other conditions. Diagnosis of DIC therefore requires careful consideration of both the clinical and the laboratory findings, with no single finding being pathognomonic.

513
514

Figure 118-3 Algorithmic approach to disorders of secondary hemostasis. *ACT,* Activated clotting time; *DIC,* disseminated intravascular coagulation; *PIVKA,* proteins induced by vitamin K absence or antagonism; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *VWD,* von Willebrand disease; *vWF,* von Willebrand factor.


Suspected disorder of secondary hemostasis
PT, PTT (or ACT), D-dimer
PT prolonged PTT (or ACT) normal
PT normal PTT (or ACT) prolonged
PT and PTT (or ACT) prolonged
PT and PTT normal ACT prolonged
Extrinsic pathway defect
Intrinsic pathway defect
Common pathway or multiple defects
Differentials: severe thrombocytopenia, thrombopathia, hypofibrinogenemia
Differentials: early hepatic failure, early rodenticide toxicity, warfarin therapy, hereditary defect (VII)
Differentials: hepatic failure, DIC, severe vWD, anticoagulant therapy, hereditary defect (XI, IX, VIII)
D-dimer
Normal
Increased
Differentials: rodenticide toxicity, DIC, hepatic failure, anticoagulant therapy, hereditary defect
Differentials: DIC, hepatic failure
Evidence of hepatic failure?
Evidence of DIC or hepatic failure?
Evidence of hepatic failure?
Yes
No
Yes
No
Evidence of rodenticide toxicity?
vWF assay, specific factor assays
Yes
No
Pursue DIC
Evidence of DIC or hepatic failure?
Yes
No
Specific factor assay
Yes
No
Toxin/drug history? PIVKA, specific factor assays

The etiology, diagnosis, and management of DIC are discussed in Chapter 117, Hypercoagulable States.

118.7.4 Inherited Coagulopathies

The clinical severity of the various inherited coagulopathies depends on the magnitude of the factor deficiency and the exposure of the animal to trauma that may precipitate bleeding. Most animals develop bleeding within the first year of life. Mildly affected animals may not bleed until later in life, particularly if they do not undergo surgery or trauma. Similarly, factor VII deficiency tends to produce milder disease, with later onset bleeding.[19]

Inherited coagulopathies should be suspected in younger animals, especially in breeds associated with factor deficiencies, if there is a history of recurrent bleeding, and if acquired causes are ruled out or deemed unlikely. A deficiency of factor VII prolongs only the PT, whereas factor VIII and IX deficiencies (hemophilia A and B, respectively) cause prolongation of the PTT. Both tests are prolonged with deficiencies of factors I, II, and X. Diagnosis requires specific factor assays performed by specialized laboratories.[19,20]

Treatment of patients with inherited coagulopathies adheres to general principles of bleeding control. If bleeding is severe or unrelenting, factors can be provided via transfusion of plasma products. For deficiencies of factors VIII and I (fibrinogen), cryoprecipitate transfusion is the ideal plasma product, whereas cryosupernatant is ideal for deficiencies of factors II, VII, IX, X, and XI.[19,20] Where these products are not available, fresh frozen plasma is an acceptable option. Further information on management and use of plasma products can be found in Chapter 66, Transfusion Medicine.

118.8 Suggested Further Reading*

M Brooks, JL Catalfamo: Platelet dysfunction. In JD Bonagura (Ed.): *Kirk's current veterinary therapy XIII: small animal practice*. ed 13, 2000, Saunders, Philadelphia, *A review of platelet dysfunction. A good resource in that it includes excellent lists of causes of inherited and acquired thrombopathias.*

AP Carr, DL Panciera: Von Willebrand's disease and other hereditary coagulopathies. In JD Bonagura (Ed.): *Kirk's current veterinary therapy XIII: small animal practice*. ed 13, 2000, Saunders, Philadelphia, *An excellent, informative, and practical review of the disease.*

R Mischke, JA Nolte: Hemostasis: introduction, overview, laboratory techniques. In BF Feldman, JG Zinkl, NJ Jain (Eds.): *Schalm's veterinary haematology*. ed 5, 2000, Lippincott Williams & Wilkins, Philadelphia, *An overview of hemostasis and a brief discussion of the tests to evaluate coagulation.*

T Stokol: Plasma d-dimer for the diagnosis of thromboembolic disorders in dogs. *Vet Clin North Am*. **33**, 2003, 1419, *An excellent and thorough review of D-dimers that addresses fibrinolysis, the various assays for D-dimer measurement, and the applicability of D-dimers in the diagnosis of DIC and thromboembolic diseases in dogs.*

* See the CD-ROM for a complete list of references

119 Chapter 119 Thrombocytopenia

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119.1 KEY POINTS

- Thrombocytopenia is a common finding in critically ill veterinary patients.
- Thrombocytopenia results from hypoproliferation (lack of production), sequestration, consumption (utilization), and destruction of platelets.
- Platelet numbers are regulated by thrombopoietin, which is produced primarily in the liver. Monitoring of the complete blood count in critically ill patients is essential for early detection of platelet abnormalities.
- Platelet counts below 20,000 to 50,000 cells/μl may lead to clinical bleeding.
- Immune-mediated thrombocytopenia can occur as a primary disease process or secondary to drug therapy, infections, or neoplasia.
- Disseminated intravascular coagulation is an important cause of thrombocytopenia in critically ill patients.
- Various diagnostic methods are often necessary to determine the etiology of thrombocytopenia.
- Platelet transfusions are often unnecessary and can lead to complications. In addition, they are typically cost prohibitive in veterinary patients.
- Additional therapeutics are targeted at the underlying disease process(es) leading to thrombocytopenia.

119.2 INTRODUCTION

Thrombocytopenia is a common finding in critically ill veterinary patients, regardless of the diagnosis at admission. There are four primary causes of thrombocytopenia: hypoproliferation (lack of production), sequestration, consumption (utilization), and destruction. Sampling or laboratory artifact may also lead to falsely low platelet counts. The critical care veterinarian's job is to diagnose the cause of the thrombocytopenia, determine whether the platelet count is low enough to warrant intervention, and prescribe appropriate treatment. For the purpose of clarity and uniformity, thrombocytopenia will be defined here as a platelet count below the lower end of the reference range for the testing laboratory, although typical platelet numbers in dogs and cats should range from 200,000 to 800,000 cells/μl. However, certain breeds may normally have lower platelet counts in the absence of disease (i.e., Cavalier King Charles Spaniel and Greyhound).

119.3 BACKGROUND

Platelets are produced in the bone marrow from pluripotential stem cells under the influence of multiple colony-stimulating factors (CSF), interleukins, and hormones. In 1994, a gene encoding a protein that stimulates platelet production was cloned. The protein is called *thrombopoietin*. Produced in the liver, kidneys, brain, and testes, thrombopoietin is released constitutively and has several roles during platelet development. In vitro it increases megakaryocyte size and number and stimulates expression of platelet-specific cell surface markers. Because platelets are responsible for binding and removing thrombopoietin, thrombocytopenia leads to increased circulating levels of thrombopoietin, and therefore greater bone marrow stimulation. Conversely, thrombocytosis results in reduced circulating thrombopoietin and, subsequently, less bone marrow megakaryocyte production.[1]

Platelets are not only important for hemostasis, but they also have a role in the inflammatory process and response to infection in normal humans and animals. The granules of platelets contain chemokines, growth factors, histamine, and serotonin. Platelets also are able to generate eicosanoids that mediate inflammation and hemostasis. Inflammation or contact with infectious agents can stimulate aggregation and degranulation of platelets. Thus platelet function in sepsis and critical illness can be both beneficial and detrimental to the patient.[2-5]

Manual evaluation of the blood smear is an effective means of estimating platelet numbers before receiving an automated count (see Chapter 122, Blood Film Evaluation). Platelet counts are easily and rapidly estimated by evaluating the blood smear. There are normally 8 to 15 platelets per 100× oil-immersion monolayer field. This correlates with circulating platelet numbers between 200,000 and 800,000 cells/µl. If platelets are clumped on the blood smear, the distribution is uneven so that a manual estimate is inaccurate. Accordingly, the automated count will also be inaccurate. Cat platelets tend to clump together, leading to falsely low reported platelet counts. Overlap of cell size between feline red blood cells and platelets can also lead to falsely reduced platelet numbers when automated cell counters are used.[6] When thrombocytopenia is reported in a feline patient, a blood smear should be evaluated (ideally by a clinical pathologist to confirm the result).

119.4 INCIDENCE AND MECHANISMS OF THROMBOCYTOPENIA

It is reported that thrombocytopenia occurs in as many as 41% of critically ill human trauma patients[2] and 18% to 35% of patients with other conditions in intensive care units.[5,7] The thrombocytopenia does not always require intervention, but it certainly warrants monitoring and attention in an attempt to prevent bleeding episodes.

The mechanisms of thrombocytopenia include hypoproliferation (lack of production), sequestration, consumption (utilization), and destruction (see Table 122-2). Sampling or laboratory artifact may also reveal falsely low platelet counts.

119.4.1 Decreased Production

Decreased platelet production occurs secondary to bone marrow dysfunction. This may be a primary disorder (from neoplastic infiltration, immune-mediated megakaryocyte destruction, fibrosis, or myelophthisis), iatrogenic causes (e.g., drug therapy including chemotherapy, estrogen, or chloramphenicol), or secondary to disease states (such as FeLV, *Ehrlichia canis* or *E. platys* infection, or hypothyroidism). There are no published reports of naturally occurring thrombopoietin deficiency in veterinary patients, but this could theoretically occur in animals with severe liver dysfunction. Critically ill patients may have cell count abnormalities of multiple lines due to cytokines, infection, and sepsis. The low platelet count must be evaluated in the context of the entire patient, the complete blood count, and a thorough evaluation of the blood smear. Review of the patient's bone marrow can help diagnose bone marrow neoplasia, fibrosis, and bone marrow toxicity. Antimegakaryocyte antibody testing on the bone marrow may also be useful in animals with immune-mediated destruction of platelet precursors. Bone marrow aspiration generally is safe in animals with severe thrombocytopenia, but pressure should be applied to the aspiration site for 5 to 10 minutes following the procedure to prevent excessive bleeding.

119.4.2 Consumption, Sequestration, and Dilution

Platelet counts will decrease when there has been significant hemorrhage, for example, in trauma patients or those with vitamin K antagonist toxicity. Massive blood product transfusions, with or without hemorrhage, can have a dilutional effect on platelet counts, as can resuscitation with any fluid that is devoid of platelets. Various disease states may result in hypersplenism and sequestration of platelets within the spleen. Typically, treating the underlying problem should resolve the thrombocytopenia without requiring direct intervention for the low platelet count.

Disseminated intravascular coagulation (DIC) develops secondary to numerous inflammatory or neoplastic diseases and leads to excessive formation of thrombin and activation of the fibrinolytic system (see Chapter 117, Hypercoagulable States). DIC is a continuum of thrombosis and fibrinolysis in small vessels, with subsequent consumption of clotting factors and platelets. The laboratory manifestations include prolongation of the prothrombin and partial thromboplastin times, thrombocytopenia, elevated fibrin and fibrinogen degradation products, and positive D-dimer levels. Thromboelastography has also been used to diagnose hypercoagulable states. Almost any severe disease state can induce the cytokine-mediated processes that lead to DIC. Management of DIC includes supportive care with appropriate blood products, and anticoagulants and, most importantly, treatment of the underlying disease.

119.4.3 Destruction of Platelets

119.4.3.1 Drug-Induced Thrombocytopenia

Many drugs that do not affect the bone marrow or coagulation directly have been associated with reduced platelet counts. These include furosemide, histamine-2 receptor blockers, cephalosporins, penicillins, trimethoprim-sulfa, quinines, and many cardiac medications. Unfractionated heparin may cause an immune-complex deposition and activation of platelets in humans that leads to a well-documented syndrome of thrombosis and necessitates discontinuation of the drug. This syndrome has not, however, been reported in small animals. Most of our patients receive multiple drugs, making it nearly impossible to clearly implicate any one medication as the sole cause of thrombocytopenia. Most of the evidence for drug-induced thrombocytopenia is anecdotal, and good clinical judgment must be used when altering therapeutic protocols for patients based on the presence of thrombocytopenia.

Because of the nature of veterinary referral medicine, it is often difficult to prove that the patient's platelet count was normal before initiation of drug therapy.[8] Multiple mechanisms for drug-induced immune responses are directed at platelets. These include drug-specific antibodies that recognize the drug on coated platelets, complexes of drug and platelet membrane glycoproteins that are seen as haptens and induce an antibody response, drugs causing conformational changes in platelet surface proteins that are then recognized by antibodies, and immune complex reactions.[9] In a review of the human case report literature, level I evidence for drug-induced thrombocytopenia was shown for many medications used in veterinary critical care, including digoxin, acetaminophen, trimethoprim-sulfa, vancomycin, diazepam, chlorpromazine, and cephalothin. Level II evidence was found for procainamide, ranitidine, ibuprofen, ampicillin, fluconazole, captopril, and oxytetracycline, among others.[8]

119.4.3.2 Immune-Mediated Thrombocytopenia

Immune-mediated thrombocytopenia or immune thrombocytopenia (ITP) can be either primary (with no underlying cause) or secondary to an infectious, inflammatory, or neoplastic disease. ITP has been associated with rattlesnake envenomation and, as discussed above, many drugs. The disease is seen primarily in dogs but also has been described in cats. In both primary or secondary ITP, platelet destruction is mediated by antiplatelet antibodies that attach to platelet antigens. The antigen-antibody complex is then removed by tissue macrophage Fc receptor–mediated phagocytosis or complement-mediated lysis.

In the critical care setting, patients often have platelet counts low enough that spontaneous, life-threatening hemorrhage is possible. It is difficult to predict which patients will bleed, regardless of the degree of thrombocytopenia. However, platelet counts must drop to less than 20,000 to 50,000 cells/µl before bleeding occurs (assuming the platelet function is normal). These patients often develop petechiae and ecchymoses, gingival bleeding, epistaxis, melena, hematochezia, hematemesis, and/or hematuria. Additionally, many of these patients may suffer from vomiting, weakness, lethargy, and dyspnea. Animals with infectious diseases causing thrombocytopenia may also have fever, lymphadenopathy, and splenomegaly.

These patients require cage rest and close monitoring during medical treatment and stabilization. Jugular venipuncture or subcutaneous and intramuscular injections should be avoided to prevent further bleeding. Diligent monitoring of the patient's cardiovascular status and hematocrit is important, and clinical anemia should be treated with red blood cell transfusions. Platelet transfusions, although rarely necessary, are indicated in animals with thrombocytopenia-induced life-threatening hemorrhage (see Chapter 66, Transfusion Medicine). Platelet transfusions are not recommended solely to increase the platelet count in patients with ITP, 516 because platelet autoantibodies will attach to the transfused platelets as readily as the patient's own platelets, 517 therefore causing premature removal from the circulation. In humans with ITP, as many as 10 units of platelet concentrate may be required every 4 to 6 hours to maintain counts around 10,000/µl.[10,11] This therapy is impractical and not well-studied in veterinary medicine, even in the most advanced critical care units.

The treatment for ITP, primary or secondary, involves suppression of the immune system so that the platelets produced are not destroyed. The most commonly prescribed chemotherapeutics include glucocorticoids, azathioprine, and cyclosporine. These drugs are used either alone or in combination for immunosuppression (see Chapter 193, Complications of Chemotherapeutic Agents). Animals with possible rickettsia-induced thrombocytopenia should also be treated with doxycycline (10 mg/kg q24h) pending titer results.

Glucocorticoids are the most commonly prescribed initial agents used to treat ITP. These drugs increase lymphoid tissue involution and reduce the phagocytic, chemotactic, antigen-processing, and intracellular killing responses of leukocytes. They also modulate many cellular responses to inflammatory mediators. Gastrointestinal (GI) protectants are recommended in animals treated with glucocorticoid immunosuppression. Animals should be monitored for evidence of GI bleeding. Dosage ranges vary, from 2 to 4 mg/kg q24h (divided 2 to 3 times per day) for oral prednisone therapy.

Azathioprine interferes with the metabolism of immune cells, reducing their cytotoxic abilities. It can lead to profound bone marrow suppression and should be used cautiously and with close monitoring. Acute pancreatitis or hepatotoxicity are also possible with this drug. The dosage most commonly prescribed is 2 mg/kg PO q24h or q72h. It may take one to several weeks of azathioprine therapy before it is fully effective. For this reason, prednisone often is started concurrently.

Cyclosporine inhibits the activities of lymphocytes, including T-helper and T-suppressor cells. Production and release of many cellular mediators by the T cells is reduced by the drug. It is available in oral and injectable forms and the dosages differ based on bioavailability. Treatment is typically initiated at 10 mg/kg PO q24h in conjunction with prednisone, or prednisone with or without azathioprine, depending on the severity of the thrombocytopenia. The medications are tapered one at a time, beginning with the steroid, when the platelet count is maintained in the normal range for at least 4 weeks. Each reduction in drug dosage or frequency should be followed with a recheck platelet count in approximately 2 to 4 weeks, depending on the patient, until the lowest effective dosage with the least objectionable side effects has been reached. Eventually, all drugs may be withdrawn, although some patients require long-term therapy. The length of time to taper the medications varies among patients based on the severity of disease and response to treatment. Regular monitoring of the complete blood count, as well as platelet count, is essential because the drugs prescribed can affect all blood cell lines. It is appropriate to check chemistry panels periodically, because these medications may have effects on hepatic and renal function. It is recommended that the clinician thoroughly reviews of these drugs and their use in combination before administering them to patients.

In severely thrombocytopenic patients who are at risk for bleeding, vincristine may be administered. This drug interferes with some immune system effects on platelets and also causes megakaryocytes to fragment into functional platelets more quickly. One veterinary study found that platelet counts in dogs given vincristine (0.02 mg/kg IV) and prednisone at the initiation of treatment reached 40,000/μl sooner than dogs that were not given concurrent vincristine. These dogs were also discharged from the hospital sooner, although the long-term outcomes were not compared.[12]

Additional chemotherapeutics that have been used include cyclophosphamide (200 mg/m^2 IV q24h), danazol (5 mg/kg PO q12h), and immunoglobulin G (0.5 g/kg IV over 6 hours).

119.5 PLATELET TRANSFUSIONS

Platelet transfusions may be necessary to treat thrombocytopenic patients that are actively bleeding or at risk of serious bleeding. When platelet counts fall below 20,000 to 50,000 cells/μl, primary hemostasis is impaired and mucosal bleeding times commonly are prolonged. However, surgical bleeding does not usually occur until platelet counts are less than 50,000/μl, and spontaneous bleeding does not typically occur until platelet counts are less than 20,000/μl. If platelet function is impaired or other components of the coagulation pathways are compromised, the actual platelet count becomes less relevant and bleeding may occur despite platelet counts greater than 50,000/μl.

Blood components containing platelets are prepared from fresh whole blood that has been collected within 8 hours and stored at room temperature. The donor blood is collected in citrate-phosphate-dextrose-adenine (CPDA) anticoagulant and centrifuged at 2000 *g* for 3 minutes. The platelet-rich plasma is then removed from the cells, kept at room temperature, and transfused within 24 hours of collection at a rate of 10 to 20 ml/kg IV over 2 to 4 hours. An additional centrifugation step of the platelet-rich plasma will yield a platelet concentrate. Although cryopreserved platelets are currently available for use in dogs, there is insufficient information to document their efficacy or to recommend routine use of the product. Research is currently ongoing.

Risks associated with platelet transfusions are similar to those of other blood products. They include infections, hypersensitivity reactions, and graft-versus-host immune responses. Clinical signs may be mild, such as an elevation in temperature or vomiting, or severe, such as life-threatening anaphylaxis. There is little, if any, evidence-based literature to guide veterinarians in the use of platelet transfusions; therefore clinical judgment is the main criterion. A human consensus conference on platelet transfusions advised that the patient's clinical picture (i.e., risk of bleeding, need for procedures, evidence of bleeding) be considered more strongly than actual platelet counts when determining a patient's need for platelet transfusion therapy. The group called for more prospective randomized trials, with protocols clearly defined, to provide evidence for safer and appropriate platelet transfusion practices.[13]

Future therapies for animals with severe thrombocytopenia may include lyophilized platelets, infusible platelet membranes, red blood cells bearing arginine-glycine-aspartic acid ligands, fibrinogen-coated albumin microcapsules, and liposome-based agents.

119.6 SUGGESTED FURTHER READING*

RH Aster: Drug-induced immune cytopenias. *Toxicology*. **209**, 2005, 149, *A review of the current understanding of mechanisms behind drug-induced immune-mediated platelet destruction*.

K Kaushansky: Thrombopoietin. *New Engl J Med*. **339**, 1998, 746, *A review of the functions, actions, and molecular biology of thrombopoietin; includes information on clinical trials of recombinant human thrombopoietin at the time of its publication*.

MHF Klinger, W Jelkmann: Role of blood platelets in infection and inflammation. *J Interferon Cytokine Res*. **22**, 2002, 913, *An excellent review of the functions of platelets other than their involvement in hemostasis*.

DF Norfolk, PJ Ancliffe, M Contreras, et al.: Consensus conference on platelet transfusion, Royal College of Physicians of Edinburgh, November 27-28, 1997. *Br J Haematol*. **101**, 1998, 609, *A synopsis of the background papers presented and the final statement of findings and recommendations from a consensus conference reviewing platelet transfusion practices*.

JL Vincent, A Yagushi, O Pradier: Platelet function in sepsis. *Crit Care Med*. **30**(suppl), 2002, S313, *A review of the function of thrombocytes in sepsis through a review of the literature*.

* See the CD-ROM for a complete list of references

120 Chapter 120 Anemia

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120.1 KEY POINTS

- Anemia is one of the most common problems in the emergency setting and despite not always being acute, it often requires immediate supportive care.
- Although the clinical signs may suggest anemia, routine and specific laboratory tests generally are needed to further define the severity, type, and cause.
- Although (peracute) acute external blood loss anemias are generally easy to identify, internal hemorrhage, hemolysis, and bone marrow failure are other important mechanisms that may not be readily evident.
- The specific underlying cause(s) of any anemia should be determined to formulate an accurate prognosis and therapeutic plan, albeit supportive care is started immediately.
- Whenever possible, appropriate blood samples (ethylenediaminetetraacetic acid, serum, and citrate tubes with adequate volumes) should be collected before any therapeutic intervention, to help reach a definitive diagnosis.
- A low packed cell volume and total protein level classically are seen following external blood loss, and animals with hemolysis typically have a normal to high serum total protein level and hyperbilirubinuria, with or without hemoglobinemia or hemoglobinuria.
- A microscopic evaluation of a blood film can readily provide clues regarding the cause of the anemia and should always be part of an emergency minimum database (see Chapter 121, Acute Hemolytic Disorders).
- Although there is no specific trigger, transfusions are given based on the assessment of clinical signs, rapidity of onset, severity, progression, and underlying cause(s) of the anemia (see Chapter 66, Transfusion Medicine).
- Severely anemic animals with serious clinical signs will likely benefit from blood type–compatible packed red blood cells (RBCs), whole blood transfusions, or alternative oxygen carrying fluids.

120.2 INTRODUCTION

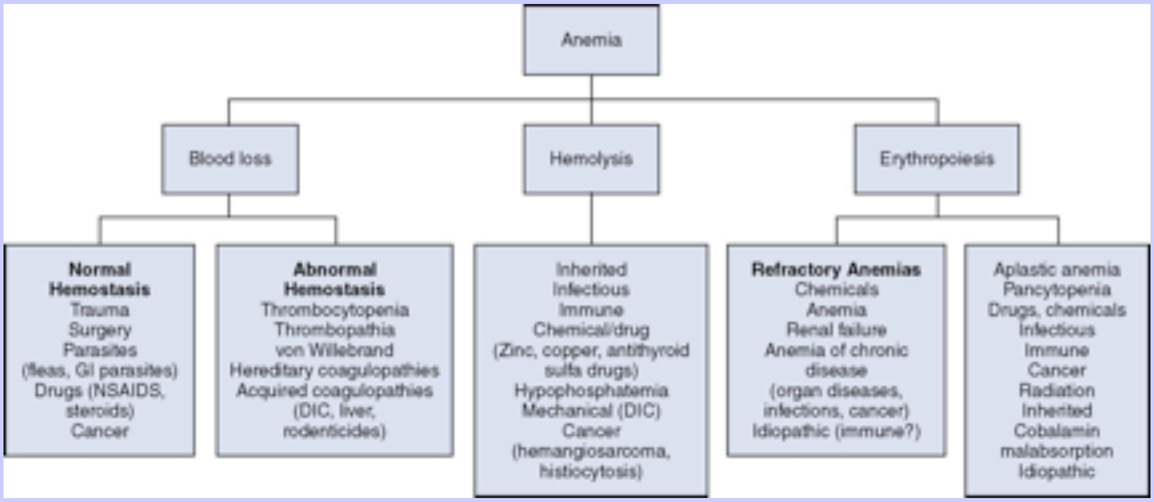
Anemia is defined as a reduction in the oxygen carrying capacity of blood due to decreases in hemoglobin (Hb) concentration and red blood cell (RBC) volume. It is certainly one of the most common laboratory test abnormalities in small animals, particularly in an emergency setting. However, anemia is not a diagnosis and thus further clinical investigations are indicated to define the underlying cause. The three mechanisms leading to anemia are blood loss, hemolysis, and reduced erythropoiesis (Figure 120-1).[1-3]

Although anemia may result from primary hematologic disorders, it is much more often associated with other organ disorders. This chapter will discuss the clinical approach to, and general therapeutic principles of, an anemic animal for the critical care clinician, and specific hematologic disorders or problems are addressed in more depth in other chapters (see section titled Hematologic Disorders).

120.3 SIGNALMENT AND HISTORY

The breed of the patient may be of particular importance now that many hereditary blood diseases and genetic predispositions in certain breeds have been recognized (e.g., immune-mediated hemolytic anemia [IMHA] in Cocker Spaniels). Although many hereditary erythrocyte defects,[2,3] coagulopathies (e.g., hemophilia A and B, factor VII or XI deficiency), von Willebrand disease, and thrombopathias lead to anemia in juvenile animals, some may be recognized only in the older animal after acute, and possibly recurrent, episodes of bleeding have occurred.[2,4,5] Furthermore, most hereditary disorders are observed in equal proportions in both genders, although hemophilia A and B, two serious coagulopathies, affect only male animals (X-chromosomal recessive trait).

Figure 120-1 Classification of anemias (also see other chapters in this section for more details). *DIC,* Disseminated intravascular coagulation; *GI,* gastrointestinal; *NSAIDs,* nonsteroidal antiinflammatory drugs.



A carefully taken history and review of previous laboratory test results can often provide clues as to the duration and cause of the anemia. For instance, depending on the geographic location and travel history, exposure to a certain infectious agent such as *Babesia, Ehrlichia, Leishmania,* and *Leptospira* spp in dogs and various viral (feline leukemia virus, feline immunodeficiency virus, and feline infectious peritonitis) and bacterial (*Mycoplasma haemofelis,* other *Mycoplasma* spp) and parasitic *(Cytauxzoon felis)* infections in cats (as well as other emerging infectious diseases) may require diagnostic testing by serology, antigen assay, or polymerase chain reaction test. There are heavy metals (zinc and copper) and other chemicals (anticoagulant rodenticides), drugs (e.g., antithyroid drugs [cat], estrogens [dog], heparin, warfarin, aspirin), and even food components (onions, garlic) that represent known triggers of anemia (see Intoxications section). A history of anemia, hemorrhage, icterus, or requirement for transfusion therapy may indicate a recurrent problem. Finally, some concurrent chronic illnesses and organ disorders, such as renal and hepatic failure, diabetes mellitus, or adverse effects of medical therapy (e.g., chemotherapeutics and many other drugs, hypophosphatemia induced by insulin administration, or hyperalimentation) may lead to severe anemia.

120.4 CLINICAL SIGNS

The clinical signs of anemia vary greatly depending on the rapidity of onset, type, and underlying cause. It is of utmost importance to determine if hemorrhage, hemolysis, or a hematopoietic production disorder is causing the anemia. Any form of anemia may be associated with pallor, and this may be the only sign in some animals. However, characteristic signs such as hemorrhage with blood loss–induced anemia (Table 120-1) or icterus or pigmenturia with hemolytic anemia may help the clinician determine the etiology.

Table 120-1 Hematologic and Physical Examination Changes With Anemia From External Blood Loss[*]

Parameter	Peracute	Acute	Chronic
Onset	Minutes to hours	Hours to days	Weeks to months
Hct/PCV	N	↓	↓↓↓
MCV	N	N to ↑	↓↓
MCHC	N	N to ↑	↓↓
Reticulocytes, polychromasia	N	N to ↑↑	↑↑
Capillary refill time	↓↓	↓↓ to N	N
Skin turgor	N	↓ to N	N
Serum iron[‡]	N	N	↓↓
WBCs	↑	↑	N or ↓
Platelets	N to ↓	↓ to ↑	↑↑

Hct, Hematocrit; *MCHC,* mean corpuscular hemoglobin concentration; *MCV,* mean cell volume; *N,* Normal; *PCV,* packed cell volume; *WBC,* white blood cell; ↓, decreased; ↑, increased.

In animals with peracute blood loss, the clinical signs are mostly related to hemorrhage and hypovolemia (hypovolemic shock), and animals with acute and chronic anemias display the more typical signs (e.g., lethargy, pallor, tachycardia, tachypnea). External blood loss is often readily evident, except for animals with gastrointestinal (GI) hemorrhage originating from the nasopharynx to the rectum. In contrast, internal hemorrhage may be hard to localize, especially in animals with retroperitoneal or deep muscle hemorrhage. A single site of hemorrhage may occur secondary to a local process such as trauma or surgery (e.g., a single lacerated vessel, hematomas), 519 520 but may also be caused by an underlying bleeding tendency. Surface hemorrhage, such as petechiations and ecchymoses, suggest a platelet disorder (thrombopathia or thrombocytopenia), whereas multiple or recurrent hematomas and intracavitary hemorrhage indicate a coagulopathy. von Willebrand disease and hereditary coagulopathies occur commonly in dogs.

Icterus may be observed the day after substantial hemolysis and the serum bilirubin concentration often exceeds 2 mg/dl. However, pigmenturia due to hyperbilirubinuria, and less commonly hemoglobinuria, is noted earlier in the disease process, even with mild hemolytic disease. It should be noted that animals with IMHA may have a combination of cholangiohepatic and hemolytic processes that result in severe icterus. Finally, cyanosis is not a clinical sign of anemia except in the presence of methemoglobinemia associated with oxidative injury to the RBCs, such as acetaminophen toxicity in cats. There must be approximately 5 g/dl of unoxygenated Hb in the capillaries for the blue color of cyanosis to be appreciated clinically; therefore severely anemic animals with severe hypoxemia may not appear cyanotic despite severe concurrent hypoxemia when having concurrent cardiopulmonary disease. The tissue hypoxia caused by anemia also activates a series of compensatory mechanisms that result in the typical signs of anemia and include[1]:

- Immediate shunting of blood away from tissues with low oxygen demand (e.g., skin) and toward the vital organs (i.e., brain, kidney, and heart) is accomplished by selective peripheral vasoconstriction and splenic contraction (in dogs). This will contribute to pale mucous membranes and delayed capillary refill time in patients with acute or peracute blood loss anemia. In contrast, patients with chronic anemia appear vasodilated from adaptation to local tissue hypoxia.
- There is an augmentation of cardiac output, initially via an increase in heart rate and subsequently by cardiomegaly. This serves to increase the supply of well-oxygenated blood to hypoxic tissue. A mild systolic flow murmur may be heard as a result of changes in blood rheology.
- Oxygen delivery is enhanced by a reduction in Hb-oxygen affinity (i.e., a right shift in the Hb-oxygen dissociation curve) caused by increased metabolic acidity (Bohr effect), and also an increased concentration of 2,3-diphosphoglyceride in RBCs (dogs only).
- Animals with any kind of anemia, but particularly those with acute anemias, will show decreased activity levels, exercise intolerance, lethargy, and possibly even collapse; they should be handled gently because they may decompensate rapidly.
- Finally, the erythropoietin-mediated accelerated erythropoiesis takes its maximal effect after about 5 to 7 days (see Laboratory Tests later in this chapter).

Although the signs of acute anemia are generally caused by blood loss or hemolysis and can be dramatic, signs associated with chronic anemia are more subtle: these animals have had time to compensate and adapt to the lower oxygen carrying capacity, at least until they are stressed, such as at the time of admission to a clinic (see Table 120-1). Furthermore, the signs of anemia may be characterized with specific signs of the underlying disease. It is not uncommon for dogs with IMHA to have an acute history of GI signs, recent vaccination, or fever.

* With internal blood loss, some changes related to iron values are not observed.

† 20% of the blood volume and unrelated to any primary or secondary hemostatic defect.

120.5

LABORATORY TESTS

Clinical signs may be strongly suggestive of anemia, but laboratory tests generally are needed to further define the severity, type, and cause of the disorder.[3,6,7] The minimal laboratory database obtained in an emergency setting certainly provides a lot of information, but additional tests are often needed. Hence it is advisable to collect more samples than are immediately necessary before instituting therapy whenever possible. However, it is important not to delay critical life support, induce major stress to the patient, or cause significant additional blood loss in the severely hypovolemic, anemic animal.

In any case of suspected anemia, it is advisable to draw blood into a serum, citrate, and ethylenediamenetetraacetic acid (EDTA) tube (tilt 5 to 10 times immediately upon collection) and to provide adequate hemostasis at the site of venipuncture, because a hemorrhagic tendency may be present. Samples from a catheter line are prone to be diluted with heparin-saline flush, which particularly affects coagulation study results. Adequate presample volumes and proper technique are therefore paramount when obtaining blood samples from indwelling catheters.

Microhematocrit tubes that generally can be used even in the tiniest patients provide invaluable information, such as packed cell volume (PCV), buffy coat, total protein concentration, and plasma color. Furthermore, before centrifugation of the microhematocrit tube, a drop of blood can be placed on a slide or used for chemistry analyses. It should be reiterated that in cases of acute anemia, various hematologic parameters will not change for hours to days, until fluid shifts from other compartments have occurred or fluid therapy has corrected the hypovolemia. However, a low PCV and total protein level are typically seen with blood loss, and animals with hemolysis have a normal or high total protein level and hyperbilirubinuria with or without hemoglobinemia or hemoglobinuria.

Microscopic examination of a blood smear can readily provide important clues regarding the type and cause of the anemia and should therefore be part of any emergency minimum database (see Chapter 122, Blood Film Evaluation).[6] Many clinicians rely solely on an instrument complete blood cell count determination, when in fact much of the necessary (and even additional) information can be gleaned from the blood smear. Abnormal instrument complete blood cell counts should always be confirmed by a blood film review.

Although initially any form of anemia is nonregenerative, polychromasia is typically seen with blood loss or hemolysis. The degree of polychromasia can be confirmed by obtaining a reticulocyte count. One point-of-care instrument offers reticulocyte counts (LaserCyte, IDEXX) in dogs and cats. An absolute reticulocyte count of less than 40,000/μl clearly indicates a nonregenerative anemia; the reticulocyte response varies depending on the duration and degree of anemia. Mild anemias may be associated with only slight increases in reticulocyte counts, whereas in patients with hemolytic and blood loss anemias of at least 5 days duration, reticulocyte counts can reach the millions/μl. The aggregate reticulocytes in cats are considered equal to the typical canine reticulocytes. Nucleated RBCs, however, are not a good parameter for regeneration in small animals because they are seen without anemia or regenerative bone marrow response, such as with lead poisoning, sepsis, neoplasia (hemangiosarcoma), and hyperadrenocorticism.

Depending on the presence or absence of a concurrent leukopenia and thrombocytopenia, the truly nonregenerative anemias (not just because of the lack of time to respond) can be separated into refractory versus aplastic anemias (pancytopenias) or extramedullary versus intramedullary disorders.[2] These additional cytopenias require confirmation by carefully reviewing the blood film at the feathered edge, because clumping can result in pseudothrombocytopenia and pseudoleukopenia. Typically 8 to 15 platelets are seen per microscopic high-power oil field, and serious bleeding concerns arise when there are fewer platelets per high-power field (<40,000/μl). One neutrophil should be identified microscopically on every third field, and although high white blood cell counts are expected with infection, they can also be seen with inflammation, immune-mediated disorders, and neoplasia.

A variety of RBC changes are extremely helpful in guiding the diagnosis. Severe hypochromasia is nearly diagnostic for chronic blood loss anemia that is often associated with leukopenia and thrombocytosis (unless thrombocytopenia is the cause of hemorrhage), and mild hypochromasia can be seen with any regenerative anemia because of the incomplete hemoglobinization of juvenile RBCs. The presence of schistocytes (disseminated intravascular coagulation [DIC], hemangiosarcoma), many Heinz bodies (toxic or oxidative Hb and RBC damage), RBC organisms *(Babesia, Cytauxzoon, Mycoplasma),* and marked spherocytosis (IMHA) are characteristic for certain hemolytic disorders.

Autoagglutination of RBCs is commonly found either directly in an EDTA tube or on a stained blood film from any sick dog, but is not necessarily diagnostic for IMHA. It could be caused by rouleaux formation (stacked up RBCs, rather than clumps) that often breaks up with the addition of equal amounts of saline on the slide. However, other nonspecific RBC agglutination may only disperse after carefully “washing” the blood sample (using 3 to 10 parts of [buffered] physiologic saline added to one part EDTA and blood), a process that typically is done before the direct antiglobulin (Coombs') and crossmatch testing in the laboratory. The diluted blood sample is mixed gently and centrifuged. The supernatant is discarded, and the RBC pellet is resuspended in saline, mixed, and centrifuged two more times to then examine the blood for agglutination. If the agglutination persists, it is considered “true” or “persistent” autoagglutination, which is strongly suggestive of IMHA and precludes further Coombs', blood type, and crossmatch testing. Furthermore, the presence of persistent agglutination or spherocytosis, or both, is seen with both primary (idiopathic) and secondary IMHA (see Chapter 121, Acute Hemolytic Disorders).[1]

An instrument-derived complete blood cell count with reticulocyte count and a microscopic blood film evaluation are desirable for any ill animal to expand on and confirm the initial findings in the emergency setting. Furthermore, a number of additional tests may prove helpful in the further diagnosis of the anemia. Although performing a cystocentesis may not be advisable in an animal with a bleeding tendency, a free catch urine sample may reveal pigmenturia due to hematuria (intact RBCs rarely cause major blood loss), hemoglobinuria (free Hb), or hyperbilirubinuria (hemolysis). A chemistry screen will likely identify an underlying hepatic or renal disorder and reveal the degree of hyperbilirubinemia or hypoalbuminemia. If hypophosphatemia is present, it should be recognized as the cause of, or contributing factor to, the anemia. Animals receiving insulin and hyperalimentation are at particular risk of developing hypophosphatemia.

Fecal examinations are done primarily to identify parasites such as blood-sucking hookworms and whipworms, but they will also reveal hematochezia and melena which can be a source of major blood loss. Occult fecal blood tests rarely are needed to confirm GI blood loss, but some animals have only intermittent blood loss. Positive occult blood test results may require confirmation in an animal that eats a meat-based diet. Moreover, a radiograph of the abdomen may discover a coin (U.S. pennies contain zinc if minted after 1982) or other foreign metal in the stomach causing copper-induced or zinc-induced hemolysis. Lead, however, is generally not a cause of anemia but rather increased numbers of nucleated RBCs, GI cramping, and neurologic signs. Toxicologic blood analysis can definitively diagnose a heavy metal, rodenticide, or other toxicity that is causing anemia, when indicated.

In animals with anemia, and particularly those with signs of multisystemic disease or excessive hemorrhage, further hemostatic studies are indicated, in addition to the evaluation of platelet count and size (see Chapter 118, Bleeding Disorders).[4,5] Overall hemostasis can be evaluated by a cuticle bleeding time, but this is a relatively crude and somewhat painful procedure, and thus specific blood tests for primary and secondary hemostasis are preferred. An assessment of coagulation cascades is performed easily with the inexpensive activated coagulation time or activated partial thromboplastin time (PTT) test and prothrombin time (PT). There are now point-of-care instruments that permit the assessment of PTT and PT on fresh whole citrated blood. The activated coagulation time or PTT screening tests are prolonged by any single (e.g., hemophilia A and B) or combined coagulation factor deficiencies (liver disease, rodenticide toxicity, heparin), except factor VII deficiency, which causes a prolongation of the PT only. Hereditary factor VII deficiency has been identified in many Beagles, Alaskan Klee Kais, and Scottish Deerhounds and causes a mild bleeding tendency.

Animals bleeding as a result of anticoagulant rodenticide intoxication have a severely prolonged PT as well as PTT and may also be moderately thrombocytopenic secondary to blood loss. The historically used PIVKA test (proteins induced by vitamin K antagonism or absence) is a modified PT test, but is neither more sensitive nor specific for rodenticide intoxication and thus does not offer any additional value to diagnose rodenticide-induced coagulopathies. Mild prolongations in coagulation times of 25% above a normal control or just slightly out of the normal range can be clinically important if caused by diseases such as hemophilia and other hereditary coagulopathies, vitamin K malabsorption, or even disseminated intravascular coagulation (DIC). It is crucial, however, to use a veterinary laboratory or in-clinic instrument validated for use in companion animals with established normal coagulation times, because the human parameters are considerably longer.

Because von Willebrand disease is so common in dogs, screening of an EDTA blood sample for von Willebrand factor deficiency with an enzyme-linked immunosorbent assay (ELISA) may certainly be indicated. And because these results are generally not immediately available, one might consider performing a buccal mucosal bleeding time. However, the buccal mucosal bleeding time is prolonged in animals with von Willebrand disease and other thrombopathias, including those associated with renal failure and animals that have recently received nonsteroidal agents such as aspirin. This test should be performed only if the platelet count is higher than 100,000/μl, because lower platelet counts cause longer bleeding times. Finally, in addition to schistocytosis and thrombocytopenia, a positive D-dimer or fibrin split product test and low or falling plasma fibrinogen concentration are suggestive of intravascular thrombosis such as DIC. These findings are prognostically important because they may be associated with many underlying disorders including neoplasia, sepsis, and IMHA. D-dimer assays have become available for use as point-of-care tests.

Other diagnostic tests for underlying causes of anemia include a search for infectious agents by antigen or antibody assays and neoplasia with imaging studies, as well as aspirate cytology or biopsy histopathology. In some cases, a bone marrow aspirate for cytology may be warranted to determine the cause of a nonregenerative anemia.

120.6 THERAPEUTIC PRINCIPLES

Depending on the cause, severity, and progression of the anemia, the indicated therapies vary greatly, and the recommendations for specific disease conditions are found in the correlating chapters. A few therapeutic principles related to the critically ill patient requiring emergency treatment are stated here. Whenever possible, the triggering agent is removed and the identified underlying disease is treated. Until the underlying disease is treated and the bone marrow has responded, supportive care is provided as needed.[1,4,5]

Animals with (peracute) acute blood loss generally benefit from aggressive fluid therapy to ensure vital organ perfusion before the administration of blood products to improve oxygen carrying capacity (see Chapter 65, Shock Fluids and Fluid Challenge). This should be accomplished immediately, and an associated drop in PCV is anticipated and of lesser concern until normovolemia is reached. In the case of hemorrhage, local hemostasis is provided immediately (e.g., compression, hemostat clamping, thrombin), if possible. Surgical correction of hemorrhage should likely be delayed until a hemostatic defect has been excluded and the bleeding tendency and anemia have been controlled adequately to permit safe surgery (do no more harm!).

Animals that have been poisoned with an anticoagulant rodenticide, but whose bleeding is not life threatening, will respond rapidly to parenteral or oral (as long as there is no vomiting) vitamin K_1 administration (2 to 5 mg/kg q12h.) depending on the specific toxin, amount ingested, and response to treatment (see Chapter 82, Rodenticides). In dogs with von Willebrand disease, desmopressin at a dosage of 1 μg/kg SC or IV has helped to control minor hemorrhage. This drug may also be helpful in treating other bleeding disorders (see Chapter 177, Vasopressin).

Because there is no specific transfusion trigger, the need to provide RBCs or hemostatic blood components is a clinical judgment. Generally, transfusions are administered when the PCV drops rapidly, reaches values of 20% or less, and the animal is showing signs of tissue hypoxia related to anemia. In cases of peracute blood loss, it is often difficult to transfuse RBCs fast enough because of the high viscosity of the blood. Blood product replacement is not required to completely restore normal hematologic values, but rather to return them to the level that ensures adequate oxygen carrying capacity and hemostasis. A rise in PCV to 20% to 25% and the most deficient coagulation factors to 20% of normal is often sufficient. The product selection for anemic or bleeding animals, the volume to transfuse, frequency of administration, and required blood compatibility testing procedures are described in detail in Chapter 66, Transfusion Medicine.

In animals with hemolytic anemia, it is critical not to jump to the conclusion that it must be IMHA, because there are many other differential diagnoses, including:

- Chemical-induced or oxidative-induced hemolysis by drugs, copper, zinc, onions, and hypophosphatemia
- Hereditary erythrocyte defects such as:
    - Phosphofructokinase deficiency (severe intermittent anemia: English Springer and Cocker Spaniels and mixed breeds)
    - Pyruvate kinase deficiency (continual anemia: various canine breeds; and intermittent anemia: Abyssinian, Somali, and domestic shorthair cats)
- Infectious hemolytic anemias (see Signalment and History earlier in this chapter)
- Hemolysis caused by neoplasias such as malignant histiocytosis and hemangiosarcoma

Because some of the diagnostic modalities may not be immediately available and IMHA may also be secondary to other disorders or triggers, hemolytic patients are often treated initially with prednisone (2 to 4 mg/kg 2 q12h) or an equivalent parenteral dose of dexamethasone and antibiotics until the triggering agents are removed and a definitive diagnosis is reached. In the initial treatment of IMHA, there is no need to use other immunosuppressive agents because none of them has proven beneficial and some may cause major side effects. Nevertheless, when IMHA is confirmed and no response is seen with glucocorticosteroid medications or their side effects are intolerable, consideration may be given to the use of cyclosporine, human intravenous immunoglobulin, or mycophenolate. Azathioprine has also been used, but its effect is not expected for weeks. Cyclophosphamide has not been beneficial in the acute treatment of IMHA in retrospective studies and in the only randomized clinical trial in patients with IMHA (see Chapter 121, Acute Hemolytic Disorders).

In any case of intoxication the causative agent should be removed immediately. Zinc-containing coins or other subjects lodged in the stomach may be removed endoscopically or surgically. There are few antidotes such as acetylcysteine and methylene blue for acetaminophen and other methemoglobin-inducing intoxications (see Chapter 79, Acetaminophen).

Intoxicated animals need aggressive supportive care. Antibiotics against microorganisms have to be selected carefully to target the likely organisms and prevent antibiotic resistance. Some parasites, such as *Babesia canis, B. gibsoni,* and *Cytauxzoon felis,* require treatment with very specific antiparasitic agents and the animals may remain carriers indefinitely. Flea-infested young animals that are severely anemic are handled very cautiously with a flea comb and supportive care (possibly a transfusion) before using medications. Similarly, anemic oncology patients may require a slow and more conservative diagnostic and therapeutic approach to prevent causing massive tumor lysis or cytopenias.

Lastly, animals with chronic, but decompensated, poorly or nonregenerative anemias will require supportive care for longer periods, because it is not anticipated that the bone marrow will respond quickly, even with specific treatment. They are generally normovolemic and their heart works at maximal capacity; hence any fluid and blood administration has to occur slowly so as not to cause pulmonary edema and congestive heart failure. Human erythropoietin can be beneficial in animals with anemia due to chronic renal failure and some other disorders. This drug may exert its effects beyond causing a rise in PCV, because it often results in rapidly improved well-being. However, this is a human product that might cause neutralizing antibodies with ensuing pure red blood cell aplasia.

120.7 CONCLUSION

A careful approach to the anemic animal with appropriate clinical and laboratory examinations will allow the 522
clinician to identify the cause and in return provide rewarding specific as well as supportive therapy in a critical 523
care setting.

120.8 SUGGESTED FURTHER READING*

M Brooks: Coagulopathies and thrombosis. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 5, 2000, Saunders, St Louis, 1829–1841, *Clinical and therapeutic information on secondary hemostasis*.

MB Brooks, JL Catalfamo: Platelet disorders and von Willebrand disease. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, St Louis, 1918–1929, *Clinical and therapeutic information on primary hemostatic disorders*.

BF Feldman: Nonregenerative anemia. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Elsevier Saunders, St Louis, 1908–1917.

U Giger: Regenerative anemias caused by blood loss and hemolysis. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, St Louis, 1886–1907, *Clinical and therapeutic information on blood loss and hemolytic disorders*.

* See the CD-ROM for a complete list of references

121 Chapter 121 Acute Hemolytic Disorders

Leah A. Cohn, DVM, PhD, DACVIM

121.1 KEY POINTS

- Not all hemolytic anemia (HA) is immunologically mediated; management will depend on proper identification of the etiology of hemolysis.
- Hemolysis can be caused by red blood cell (RBC) fragmentation, toxin-induced RBC damage, inherited RBC defects, infection, immune-mediated RBC destruction, or a variety of other causes.
- Distinguishing intravascular from extravascular hemolysis can be useful diagnostically and prognostically.
- Proper therapy for HA includes both supportive care (e.g., transfusion) and management aimed at the underlying cause of hemolysis.
- Immune-mediated hemolytic anemia (IMHA) may be a primary or secondary disease process. Recognition of inciting causes for secondary IMHA (e.g., infection, drugs, neoplasia) is important.

121.2 INTRODUCTION

Hemolysis is the destruction of RBCs. All RBC are destroyed eventually, but pathologic hemolysis occurs when the rate of destruction is increased and the life span of RBCs is thus shortened. HA results when regeneration of RBCs from precursor cells is inadequate to replenish the destroyed cells. HA is caused by several immunologically and nonimmunologically mediated mechanisms (Box 121-1). It is crucial for the veterinarian to distinguish among these causes of hemolysis to provide appropriate therapy.

Anemia is often classified as either regenerative or nonregenerative. Blood loss and HA are the two main causes of regenerative anemia. Realistically, regeneration of RBCs requires time, and hemolysis is often an acute process. Therefore, hemolysis that has been present for less than 3 to 5 days (dog and cat, respectively) is unlikely to be regenerative. Although hemolysis may be chronic and low grade, a drop in packed cell volume (PCV) of more than 1% per day suggests either blood loss or hemolysis. Once blood loss is ruled out (typically by an absence of detectable bleeding and the presence of a normal total protein level), hemolysis becomes more likely as the cause of a rapidly progressive anemia.

121.2.1 Evaluation of the Patient with Hemolysis

The clinical picture of the dog or cat with HA is nonspecific and may relate not only to hemolysis, but also to an underlying disease process. Although anemia due to defective or deficient RBC production is often insidious in onset, HA frequently results in an acute illness. As a result of the anemia and decrease in oxygen delivery to the tissues, owners may notice exercise intolerance, anorexia, general malaise, syncope or collapse, or pallor. On physical examination, pale mucus membranes are a characteristic finding and icterus is often noted. Other findings may include tachycardia, tachypnea, bounding pulse, and a soft systolic basilar heart murmur.

Hemolysis, which occurs predominantly extravascularly, may also occur inside the vascular space. Either way, breakdown of RBCs leads to release of bilirubin; bilirubinemia and bilirubinuria are consistent with either intravascular or extravascular pathologic hemolysis.[1] Hemoglobinemia and hemoglobinuria are found only with intravascular hemolysis. Several disease states cause both intravascular and extravascular hemolysis. When intravascular hemolysis predominates, the disease process often carries a poorer prognosis for recovery than diseases associated with predominantly extravascular hemolysis.[1]

Hemolysis is associated with numerous changes in RBC appearance, and these changes are often a key to identifying the cause.[1] There is no substitute for a thorough evaluation of a well-stained blood smear using oil immersion and high magnification; blood cell counts alone are inadequate for the evaluation of an animal with suspected hemolysis. Shape changes may point to a specific cause. For example, schistocytes suggest fragmentation, spherocytes suggest immune-mediated destruction (Color Plate 121-1), and Heinz bodies suggest oxidative damage (Color Plate 88-2). Additionally, erythrocytic parasites may be observed microscopically.

121.2.1.1 Box 121-1 Causes of Hemolysis

121.2.1.1.1 Fragmentation Hemolysis

- Disseminated intravascular coagulation
- Caudal caval syndrome
- Splenic torsion
- Heart valve disease
- Hemangiosarcoma
- Vasculitis

121.2.1.1.2 Toxicant-Induced Hemolysis

121.2.1.1.2.1 Foodstuffs and Additives

- Onion
- Garlic
- Propylene glycol

121.2.1.1.2.2 Drugs

- Acetaminophen

DL-methionine

Vitamin K

Methylene blue

Benzocaine

121.2.1.1.2.3 Chemicals

Zinc

Copper

Naphthalene

Skunk musk

121.2.1.1.3 Immune-Mediated Hemolysis

Idiopathic primary

Secondary (neoplasia, infection, drugs)

Neonatal isoerythrolysis

Transfusion

121.2.1.1.4 Heritable Hemolysis

Phosphofructokinase deficiency

Pyruvate kinase deficiency

Osmotic fragility syndromes

Nonspherocytic HA of Beagles

121.2.1.1.5 Infection-Related Hemolysis

Red blood cell infection

- *Mycoplasma haemofelis*
- *Mycoplasma haemocanis*
- *Candidatus M. haemominutum*
- *Babesia canis*
- *Babesia gibsoni*
- *Cytauxzoon felis*

Systemic infection

Feline leukemia virus

Feline immunodeficiency virus

Leptospirosis

Bartonellosis

Ehrlichia canis

121.2.1.1.6 Miscellaneous Causes of Hemolysis

Hypophosphatemia

Hemolytic-uremic syndrome

Iatrogenic changes in osmolarity

Envenomation

Histiocytic neoplasia

HA, Hemolytic anemia.

Regardless of the cause of hemolysis, certain therapeutic principles apply. Heme pigments released by hemolysis can cause nephrotoxicity in humans. Although acute renal failure resulting from hemolysis is not reported in small animals, adequate renal perfusion should be maintained to minimize this risk. Supportive care for animals with severe or rapid-onset anemia includes provision of either transfused RBCs or purified hemoglobin solution. The need for transfusion should be based on not merely an RBC count, hemoglobin measurement, or PCV but on clinical assessment (e.g., mental state, activity level, heart and respiratory rates, pulse quality). A packed RBC transfusion provides oxygen carrying capacity with less volume than whole blood and is often preferred in animals with hemolysis (see Chapter 66, Transfusion Medicine). Transfusion in cats must follow blood typing of both donor and recipient; blood typing of recipient dogs is not required for first-time transfusions or if only DEA 1.1-negative blood is transfused. Although transfusion of cross-matched blood is ideal, first transfusions in dogs and transfusion of blood-type compatible cats are usually successful without cross-matching.[2] Transfused RBCs may be susceptible to the same cause of hemolysis as native RBCs. Purified hemoglobin (Oxyglobin) solutions do not require cross-matching or blood typing, although the future availability of these products is unknown.

121.3 FRAGMENTATION HEMOLYSIS

Fragmentation of RBCs results from numerous processes, but is most commonly the result of shearing of the RBC membrane in the small vessels (microangiopathic hemolysis) or from altered rheologic forces. Because shearing typically occurs inside the vascular space, hemoglobinemia and hemoglobinuria are common findings. The observation of schistocytosis on a peripheral blood smear provides supportive evidence of fragmentation; keratocytes and acanthocytes are also frequently identified.[1] When fragmentation is suspected, diagnostic testing is aimed at identification of the underlying pathology. In a dog with a prominent heart murmur this might include an echocardiographic examination to rule out caudal caval syndrome, but the presence of marked splenomegaly would prompt ultrasonographic examination to rule out splenic torsion or neoplasia. Assays of coagulation are usually indicated because disseminated intravascular coagulation (DIC) can be a cause of fragmentation hemolysis, and because several of the conditions that lead to fragmentation hemolysis can precipitate DIC.[1] Fragmentation hemolysis is a mechanical process, and management must be aimed at correction of the underlying disease (see Chapter 117, Hypercoagulable States). Supportive care includes provision of adequate oxygen carrying capacity (e.g., RBC transfusion, Oxyglobin) and prevention of complications of hemolysis (e.g., nephrotoxicosis, DIC).

121.4 TOXICANT-INDUCED HEMOLYSIS

Much toxicant-induced hemolysis is related to oxidative injury. Oxidation of hemoglobin iron results in formation of methemoglobin, which, although unable to bind oxygen, does not shorten RBC life span (see Chapter 88, Methemoglobinemia). Oxidative membrane damage, can however, lead to intravascular (due to membrane rupture) 524 or extravascular 525 (due to premature phagocytosis) hemolysis. Oxidation of hemoglobin causes Heinz body formation which, in turn, leads to removal of RBCs. Unlike dogs, cats may have some Heinz bodies without anemia. Eccentrocytes and pyknocytes are additional morphologic changes indicative of oxidative injury.

Table 121-1 Heritable Conditions Predisposing to Hemolysis

Defect	Reported Breed Associations	Typical Clinical Picture
Osmotic fragility	Abyssinian and Somali cats, English Springer Spaniel	Intermittent moderate to severe anemia with splenomegaly (cats)
Phosphofructokinase deficiency	English Springer Spaniel, Cocker Spaniel, canine mixed breed	Exercise or excitement (panting)-induced hemolytic crises and exertional myopathy characterized by hemoglobinuria
Pyruvate kinase deficiency	Basenji, Beagle, Miniature Poodle, Toy Eskimo, Dachshund, Chihuahua, Pug, West Highland White Terrier, cats	Initial extremely regenerative mild anemia becomes nonregenerative as a result of osteosclerosis and myelofibrosis Hemosiderosis-associated hepatic failure also occurs

A variety of substances can result in toxicant-induced hemolysis (see Box 121-1). Cats are more susceptible to chemical oxidant injury than are dogs for several reasons, including differences in drug metabolism and hemoglobin structure. Therapy for toxicant-induced HA involves removal of the toxicant (when possible) plus supportive care. Clinicians should be especially alert for the presence of metallic foreign bodies within the gastrointestinal (GI) tract (e.g., pennies minted after 1982), especially in puppies and young dogs with HA, because removal of the object(s) with or without chelation therapy is curative.[3] For some oxidant toxins, other therapies are possible. For instance, N-acetylcysteine (140 mg/kg PO, then 70 mg/kg q6h for 7 treatments) is recommended for treatment of acetaminophen toxicity (see Chapter 79, Acetaminophen).[4] A therapeutic role for other antioxidants (e.g., S-adenosyl-L-methionine) in other toxicant-induced hemolytic diseases is less clearly defined.[5]

121.5 HERITABLE HEMOLYSIS

Although heritable HA is relatively uncommon, heritable defects may be common in a given breed (Table 121-1) or family. Not all hereditary erythrocyte defects lead to HA.[6] When present, hemolysis is more likely to be detected in young adults than in puppies or kittens. Clinical severity of hemolysis can range from mild and well compensated to life-threatening crisis. Inherited erythrocyte defects should be strongly considered in animals with a Coombs'-negative HA when causes of fragmentation, toxins, and infection are not identified, or in breeds known to have a high incidence of heritable hemolysis. Often, changes in RBC shape are absent except for anisocytosis signifying a regenerative anemia.[6]

Erythrocyte defects leading to hemolysis are associated with membrane abnormalities or enzyme deficiencies. The most common of these include syndromes of increased osmotic fragility, pyruvate kinase deficiency, and phosphofructokinase deficiency.[7-9] Specific testing for these causes of hereditary hemolysis can be divided into physical and functional tests of the RBC or molecular genetic tests. Physical and functional tests are available from only a few laboratories (e.g., Josephine Deubler Genetic Disease Testing Laboratory for Companion Animals at the School of Veterinary Medicine, University of Pennsylvania). Genetic tests identify breed-specific mutations. These tests are most valuable in identification of heterozygous carriers (most erythrocyte defects in dogs and cats are autosomal recessive traits). Treatment usually entails supportive care and includes cross-matched transfusion as needed.

121.6 INFECTION-RELATED HEMOLYSIS

Infection may lead to hemolysis, either as a result of direct damage to the RBCs or through indirect mechanisms. Infection of the RBCs can cause hemolysis via direct cell damage, through initiation of an immunologically mediated response to infection, or both. Systemic infections can lead to hemolysis by mechanisms, including induction of secondary immune-mediated RBC destruction or microangiopathic hemolysis. The importance of recognizing infection-induced hemolysis cannot be overstated, because it offers the potential for a cure and may avoid unnecessary and potentially harmful treatment strategies (such as immune suppression).

121.6.1 Infection of Red Blood Cells

There are few important RBC infections that cause hemolysis of dogs or cats in the United States. These include hemotropic *Mycoplasma* (formerly known as *Haemobartonella*) and the protozoal parasites *Babesia canis, Babesia gibsoni,* and *Cytauxzoon felis*.

Mycoplasma haemofelis (the causative agent of feline infectious anemia) should be a differential diagnosis for any cat with HA.[10] Presumably transmitted by fleas, the resulting hemolysis is variable in severity, cyclic in nature, and often Coombs' positive. The smaller *Mycoplasma haemominutum* seems to be less virulent than its larger cousin. Although routine microscopy often allows for identification of RBC parasites, parasite burden waxes and wanes, and hemotropic *Mycoplasma* may “fall off” RBCs in vitro. For these reasons, polymerase chain reaction is preferred to rule out infection. Doxycycline (5 mg/kg PO q12h for 21 days) is the treatment of choice, but the immune-mediated component of severe hemolysis may respond to a short course of prednisolone (2 to 4 mg/kg PO q24h). Hemotropic canine *Mycoplasma* rarely causes significant hemolysis unless there has been prior splenectomy or immune suppression.

The species of *Babesia* likely to cause HA in dogs and cats in the United States are *B. canis* subspecies *vogeli* and the Asian strain of *B. gibsoni*. Breed associations include Greyhounds and Pit Bull Terriers, respectively, so hemolysis in these breeds should result in suspicion.[11] Although both organisms are transmitted by ticks, perinatal infection, fighting, and transfusion are important means of infection in the United States. Hemolysis, thrombocytopenia, and hyperglobulinemia are common findings but are not universally present; many infected dogs appear quite healthy. As with *M. haemofelis,* microscopy is specific but not sensitive for diagnosis; polymerase chain reaction and serology are also available. The therapy of choice for *B. canis* is imidocarb dipropionate (6.6 mg/kg IM once, repeat in 2 weeks), but *B. gibsoni* is treated with a combination of atovaquone and azithromycin (13.5 mg/kg PO q8h and 10 mg/kg PO q24h, respectively, both for 10 days).

Cytauxzoon felis causes a tick-transmitted infection endemic to the southeastern, midwestern and mid-Atlantic regions of the United States.[12] Cats typically become sick in the spring or summer seasons with an acute febrile illness that is often accompanied by icterus and pancytopenia. Although HA is a part of the illness, death results from multiple organ failure as a result of vascular occlusion by schizont-laden monocytes. When monocytes rupture, they release merozoites that are then taken up by RBCs, where they are identified as *piroplasms*. Sometimes death precedes the findings of hemolysis or RBC piroplasms. There is no proven effective therapy.

121.6.2 Systemic Infections

Systemic infections may lead to hemolysis through a variety of mechanisms. Feline leukemia virus infection often leads to anemia due to ineffective RBC production, but HA also occurs in cats that are seropositive for feline leukemia virus. In some cases hemolysis may be due to hemotropic mycoplasmosis, but in others hemolysis remains idiopathic and likely immune mediated.[13,14] Likewise, feline immunodeficiency virus can lead to hemolysis.[15] Although *Ehrlichia canis* frequently causes a nonregenerative anemia, it is an infrequent cause of severe hemolysis.[16] There is some evidence that bartonellosis may result in HA in dogs.[17]

121.7 IMMUNE-MEDIATED HEMOLYSIS

Most dogs and many cats with hemolysis will eventually be determined to have immune-mediated hemolytic anemia (IMHA), wherein destruction of RBCs is mediated by antibody-triggered or complement-triggered events.[1] In some cases, an infection, drug, or cancer will be determined to have initiated the aberrant immune attack on the RBCs (i.e., secondary IMHA). Identification of such triggers profoundly affects treatment and prognosis. Signalment, history, and physical examination all guide the direction and intensity of a search for triggers of IMHA. Hemolysis in cats, in very young or old dogs, in animals with concurrent disease or drug histories, or in animals with physical examination findings not directly related to hemolysis and anemia should prompt added vigilance for explanations other than idiopathic primary IMHA.

121.7.1 Findings Suggestive of Immune-Mediated Hemolytic Anemia

IMHA occurs more commonly in dogs than cats.[14] Certain dog breeds (e.g., Cocker Spaniel) are overrepresented, as are female dogs, but any breed and either gender may be affected.[18-20] Most dogs with idiopathic IMHA are young or middle-aged adults. Unless immune attack includes RBC precursors, IMHA becomes a very regenerative anemia within a few days. Leukocytosis and thrombocytopenia are common findings in dogs with IMHA, as are hyperbilirubinemia and hyperbilirubinuria. Although there are several tests to confirm the immune-mediated nature of hemolysis, secondary as well as primary IMHAs are detected by these methods. The most common form of IMHA results from an immunoglobulin G (IgG)-mediated type II hypersensitivity reaction causing extravascular hemolysis. Phagocytic damage to the RBC membrane results in formation of highly characteristic spherocytes as seen in Color Plate 121-1 (difficult to detect in cats because of a normal lack of central RBC pallor). Less common is IMHA in which IgM or IgG mediates RBC autoagglutination. Agglutination can be seen grossly and microscopically but must be differentiated from rouleaux formation. Often, simply adding an equal volume of saline to whole blood will disperse rouleaux; if it does not, the RBCs should be washed with saline and reexamined. True autoagglutination persists despite washing; this finding confirms an immunologic component (Color Plate 121-2). The Coombs' test is helpful when spherocytosis is minimal and autoagglutination absent to confirm the immune-mediated nature of hemolysis, as may be the case in animals with intravascular hemolysis.[21] Species-specific antisera containing antibody to IgG, IgM, and complement are combined for reaction with the patient's washed RBCs; if the antibody or complement is attached to the RBC, agglutination will result. Because both false-positive and false-negative results are possible, more sophisticated tests have been developed, including flow cytometric assays for the presence of RBC-bound antibody.[22]

121.7.2 Treatment of Immune-Mediated Hemolytic Anemia

Unfortunately, there are few therapies with documented efficacy for treatment of patients with IMHA. Despite aggressive treatments many patients die.[18,19,23] Therapies can be divided into those aimed at suppression of the aberrant immunologic response, those providing supportive care, and those aimed at prevention of complications.

121.7.2.1 Immune Suppression

Glucocorticoids are the mainstay of treatment for IMHA. High-dose glucocorticoids exert multiple actions to slow immunologically mediated destruction of RBCs; response is unexpected before 3 days. Initially, prednisone or prednisolone (cats) is given at a dosage of 2 to 4 mg/kg PO q12h. Medium to large dogs should generally be treated with the lower end of the dose range (e.g., 2 mg/kg q24h) while cats may require even higher dosages (up to 8 mg/kg q24h). Equivalent dosages of other glucocorticoids (e.g., 0.2 to 0.75 mg/kg q24h IV of dexamethasone) may be substituted. Steroids are continued at high doses until the RBC count has normalized. Then, the dosage is slowly tapered (with frequent reevaluations of RBC numbers) as long as hemolysis does not recur.[24] Although there is no definitive rule for tapering, twice daily doses are usually consolidated into a single daily dose, and the total dosage is decreased by increments of 20% to 25% every few weeks until reaching 0.5 mg/kg q24h. At that point, the dose is unaltered but frequency is changed to every other day to spare the hypothalamic-pituitary-adrenal axis. Tapering can continue until the lowest effective dosage is attained or steroids are discontinued altogether. Depending on initial disease severity and response to therapy, the entire course of treatment may last from 4 to 9 months or more.

Because glucocorticoids do not always halt hemolysis and may be associated with pronounced adverse effects, other forms of immune suppression have been used (Table 121-2); for most there is no evidence to support or refute efficacy. Cyclophosphamide, however, has fallen out of favor as a result of failed efficacy.[25] Cyclosporine is an alternative immune suppressant, but a single prospective study found no positive impact on survival.[26] Intravenous immunoglobulin has been used when other treatments have failed; it may provide some short-term benefit but does not seem to improve long-term survival.[27] The most popular adjunctive immunosuppressive drug is azathioprine.[20]

121.7.2.2 Supportive Care

Supportive care for animals with hemolysis often includes the provision of adequate oxygen carrying capacity via transfusion of RBCs or Oxyglobin. The rapidity of onset of anemia may have more to do with clinical signs than the absolute degree of anemia. Tachycardia, tachypnea, weakness, bounding pulses, and hyperlactatemia are relative indicators that oxygen carrying support is required. In the past, practitioners were often reluctant to transfuse patients with IMHA for fear that transfused cells may blunt the drive to a regenerative response, or that RBC breakdown products may damage the renal tubules. There seems to be little merit to the former concern, and the latter is also unlikely and further outweighed by the need to prevent tissue hypoxia. Retrospective studies comparing outcomes of dogs receiving transfusion with those receiving Oxyglobin have produced conflicting results.[20,23] For now, availability and cost are reasonable criteria by which to make a choice between transfusion and Oxyglobin. Unless plasma is required for other reasons, packed RBCs are preferred to whole blood transfusion.

Table 121-2 Immunosuppressive Drug Regimens Used to Manage IMHA in Dogs and Cats

Drug	Starting Dosage	Important and Common Adverse Effects	Comments
Prednisone	2 to 4 mg/kg PO divided q12h or q24h Medium to large dogs typically treated with 2 mg/kg q24h; cats may require up to 8 mg/kg q24h.	PU and PD, polyphagia, panting, altered behavior	Initial dosage is tapered slowly as allowed by clinical condition
Azathioprine	2.2 mg/kg PO q24h	GI upset, myelotoxicity, hepatopathy	Initial dosage is halved in 7 to 10 days, slowly tapered
Cyclosporine	Oil-based: 10 to 25 mg/kg PO divided q12h Emulsified: 5 to 10 mg/kg PO divided q12h	GI upset, gingival hyperplasia, rarely nephrotoxicity	Trough levels must be monitored to adjust dosage
Cyclophosphamide	50 mg/m^2 q72h, PO q8-12h or 200 mg/m^2 IV once/week	GI upset, myelotoxicity, sterile hemorrhagic cystitis	Not recommended
Chlorambucil	0.1 to 0.2 mg/kg q24h	GI upset, myelotoxicity	Not recommended
Leflunomide	4 mg/kg q24h	GI upset, anemia, lymphopenia	Trough levels monitored to adjust dosage
Danazol	5 mg/kg q8-12h	Virilization, hepatotoxicity	Not recommended
Mycophenolate mofetil	20 to 40 mg/kg PO divided q8-12h	GI upset	Little veterinary experience
IVIG	0.5 to 1.5 g/kg infused IV over 6 to 12 hr	Hypersensitivity reaction	Single-use treatment in crisis

GI, Gastrointestinal; *IMHA*, immune-mediated hemolytic anemia; *IV,* intravenous; *IVIG,* intravenous immune globulin; *PD,* polydipsia; *PO,* per os; *PU,* polyuria.

121.7.2.3

Prevention of Complications

Dogs treated for IMHA die because they are euthanized or from complications (such as pulmonary thromboembolism or DIC) more often than from anemia.[19] Prevention of pulmonary thromboembolism using heparin alone has shown little success (see Chapter 187, Anticoagulants). For now, ultralow-dose aspirin (0.5 mg/kg PO q24h) is recommended either with or without adjunctive heparin therapy.[20] In addition, high-dose steroid use can result in GI ulceration. There are no studies demonstrating the need for or adequacy of any particular GI protectants in the treatment of IMHA, but a histamine-2 blocker such as famotidine or the synthetic prostaglandin misoprostol should be considered (see Chapter 181, Gastrointestinal Protectants).

121.7.3 Other Causes of Immune-Mediated Hemolytic Anemia

Transfusion reactions and neonatal isoerythrolysis result from immunologically mediated but nonaberrant attack against RBCs. Animals have unique blood types, and transfusion of unmatched blood can result in a normal hemolytic response by the host against the transfused cells. In dogs, preformed antibodies to RBC antigens are uncommon, as are hemolytic complications of non-blood typed, non-cross-matched initial transfusions. However, subsequent transfusions may result in hemolysis.[28] Because cats have preformed antibodies to RBC antigens other than their own, even first transfusion of non-blood typed, non-cross-matched blood may result in severe hemolysis (especially type B cats receiving type A blood).[29] These same preformed antibodies mediate feline neonatal isoerythrolysis. Type A or type AB kittens born to type B queens can develop HA after absorption of anti-A alloantibodies via colostrum.[30] Although most cats in the United States are type A, British Shorthair, Devon Rex, Abyssinian, and Somali cats have a high prevalence of type B blood.[29] 527

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121.8 SUGGESTED FURTHER READING*

JW Harvey: Congenital erythrocyte enzyme deficiencies. *Vet Clin North Am Small Anim Pract*. **26**, 1996, 1003, *Review discusses several congenital erythrocyte enzyme deficiency syndromes*.

B Kohn, C Weingart, V Eckmann, et al.: Primary immune-mediated hemolytic anemia in 19 cats: diagnosis, therapy, and outcome (1998-2004). *J Vet Intern Med*. **20**, 2006, 159, *Retrospective study of clinical presentation, treatment, and outcome in 19 cats with presumed primary idiopathic IMHA*.

N Mason, D Duval, FS Shofer, et al.: Cyclophosphamide exerts no beneficial effect over prednisone alone in the initial treatment of acute immune-mediated hemolytic anemia in dogs: a randomized controlled clinical trial. *J Vet Intern Med*. **17**, 2003, 206, *One of the few prospective studies evaluating a potential therapy for IMHA in dogs found no benefit to the use of cyclophosphamide over glucocorticoids alone*.

JE Sykes: Feline hemotropic mycoplasmosis (feline hemobartonellosis). *Vet Clin North Am Small Anim Pract*. **33**, 2003, 773, *Overview of the classic cause of feline infectious anemia, the organisms formerly known as* Haemobartonella *and now referred to as hemotropic* Mycoplasma.

TK Weinkle, SA Center, JF Randolph, et al.: Evaluation of prognostic factors, survival rates, and treatment protocols for immune-mediated hemolytic anemia in dogs: 151 cases (1993-2002). *J Am Vet Med Assoc*. **226**, 2005, 1869, *Retrospective evaluation of a large group of dogs with IMHA. Discusses clinical characteristics on presentation, treatment, and mortality with some emphasis on prevention of thromboembolic complications. The best survival associated with a combination of glucocorticoids, azathioprine, and ultra-low-dose aspirin*.

* See the CD-ROM for a complete list of references

122 Chapter 122 Blood Film Evaluation

Alan H. Rebar, DVM, PhD, DACVP

122.1 KEY POINTS

- Blood film evaluation provides both general information regarding the health status of emergent and critically ill patients and specific diagnostic information in the case of true hematologic emergencies. It is therefore an essential component of the workup for all emergency and critical care patients.
- Blood film evaluation requires a systematic approach. The various cellular elements of the blood (leukocytes, erythrocytes, platelets) should be examined in the same order and manner on every blood film.
- Leukocyte morphology is used to recognize and characterize inflammatory disease. Signposts of inflammation are a neutrophilic left shift, monocytosis, or a persistent eosinophilia. Regenerative left shifts (high neutrophils, increased bands) indicate that bone marrow response is keeping pace with tissue demand; degenerative left shifts (low or normal neutrophils, increased bands) indicate that tissue demand is overwhelming the bone marrow (guarded prognosis).
- Neutrophil toxicity indicates either the presence of circulating toxins interfering with neutrophil development in bone marrow or accelerated neutrophil production. Neutrophil toxicity is most commonly (but not exclusively) associated with bacterial infection.
- Lymphocyte patterns and morphology are also important in critically ill patients. Low lymphocyte numbers are generally a reflection of stress (high circulating corticosteroids). Reactive lymphocytes indicate antigenic stimulation.
- The critical step in evaluating anemias is classifying them as regenerative or nonregenerative based upon the presence (regenerative) or absence (nonregenerative) of increased numbers of polychromatophils on the blood film. Regenerative anemias are due to blood loss or hemolysis, whereas nonregenerative anemias have a broader range of causes.
- In highly regenerative anemias, red blood cell morphology is extremely important, because it may indicate a specific hemolytic disease. Immune-mediated hemolytic anemia (IMHA), Heinz body hemolytic anemia, mycoplasmosis, and babesiosis, among others, are all hemolytic diseases that can be diagnosed largely on the basis of red blood cell morphology.
- Thrombocytopenia is the most common primary cause of bleeding disorders in dogs and cats. Thrombocytopenia can result from sequestration of platelets in an enlarged spleen (rare), peripheral utilization in severe inflammation (clinical or subclinical disseminated intravascular coagulation [DIC]), immune-mediated peripheral destruction (immune-mediated thrombocytopenia [ITP]), or lack of production in the bone marrow.
- Myeloid and lymphoid leukemias can come to medical attention in various stages of disease, so peripheral blood findings are variable from patient to patient. Severe nonregenerative anemia is the most consistent finding. White blood cell findings are highly variable.

122.2 INTRODUCTION

Hematologic abnormalities are among the most common findings in emergent and critically ill patients. Regardless of whether these abnormalities represent primary diseases affecting the hematopoietic system or secondary manifestations of underlying disease in a different organ system, they can usually be recognized through blood film evaluation. Blood film evaluation is therefore an essential component of the clinical workup of all emergent and critically ill patients. This chapter presents a systematic approach to blood film preparation and examination, and highlights the more important hematologic abnormalities seen in the critically ill dog or cat.

122.3 BLOOD FILM PREPARATION

To obtain blood films of consistent quality, the same technique must be used every time. A drop of well-mixed blood (blood collected in ethylenediaminetetraacetic acid [EDTA] is often preferred) is placed near the frosted end of the first slide. A second slide (the spreader slide) is placed at about a 30-degree angle to the first and drawn back until it touches the drop of blood. The drop is allowed to spread along the entire edge of the spreader slide by capillary action. At this point the spreader slide is moved quickly and smoothly across the full length of the first slide. The finished blood film is allowed to air dry before staining using a standard Romanowsky technique (Wright stain or a modified quick stain). A well prepared blood film is flame shaped.[3]

122.4 BLOOD FILM EVALUATION

A systematic approach to blood film evaluation is critical to obtaining accurate and complete results. Blood films should first be scanned at low magnification (10× to 20×). All three areas of the blood film (the body of the film near the drop, the monolayer where red blood cells are seen as individuals and may touch but do not overlap, and the feather edge which is most distant from the drop) should be examined. Scan for clumping of cells (platelets, white blood cells, or red blood cells), rouleaux (orderly stacking of red blood cells), and agglutination (three-dimensional clumping of red blood cells). Any atypical cells or organisms (parasites) should be noted.[3]

Cell morphology is assessed in the monolayer. Even at scanning magnification, one can estimate total white blood cell count and differential. Typical appearance of each leukocyte cell line (neutrophil, eosinophil, monocyte, and lymphocyte) can be assessed. Individual red blood cells can be evaluated for evidence of anisocytosis, polychromasia, and poikilocytosis.

After the slide has been scanned, the entire process should be repeated at oil immersion magnification (100×). Again, most of the evaluation is done in the monolayer. Leukocytes are evaluated for morphologic detail. The presence of neutrophil toxicity, reactive lymphocytes, and inclusions in neutrophils and monocytes are noted. A left shift, which can be recognized at scanning magnifications, is confirmed at oil immersion magnification.

Red blood cell changes suspected at scanning magnification (anisocytosis, polychromasia) also can be confirmed. Poikilocytosis is best assessed at oil immersion magnification. The various types of poikilocytes (spherocytes, schizocytes, acanthocytes, dacryocytes) can all be recognized. Red blood cell inclusions, such as Heinz bodies, and red blood cell parasites, such as *Mycoplasma* and *Babesia,* can be observed.

Oil immersion magnification is best for evaluating platelet numbers. In general, in the monolayer there should be 8 to 15 platelets per 100× field. This number can be reduced significantly, despite a normal platelet count, if platelet clumps are present.

122.5 WHITE BLOOD CELL RESPONSES[1,3]

White blood cell responses are among the best laboratory the indicators of the general health status of critically ill patients. Many emergent and critically ill patients suffer from inflammatory diseases. Inflammation is usually indicated by the leukogram. Signs of inflammation include a left shift, monocytosis, or persistent eosinophilia. General patterns of leukocyte responses are found in Table 122-1.

Left shifts (increased numbers of immature neutrophils in the blood) can be further classified as regenerative or degenerative, depending upon whether total neutrophil counts are increased or decreased. Increased numbers of mature neutrophils in conjunction with a left shift is a regenerative left shift (Color Plate 122-1). Regenerative left shifts indicate that bone marrow production of neutrophils is keeping pace with tissue demand, which results in a favorable prognosis for the patient. In contrast, degenerative left shifts have normal or decreased numbers of mature neutrophils, indicating that marrow production is not keeping pace with tissue demand. This in turn leads to a guarded prognosis for the patient. A special form of degenerative left shift occurs when total neutrophil counts are increased, but over 50% of the neutrophils are immature.

Monocytosis (Color Plates 122-1 and 122-2) not only indicates inflammation, but is also an indicator of demand for phagocytosis or tissue necrosis. Monocytosis can occur acutely or chronically depending on the inciting cause of the inflammation. Acute systemic diseases such as histoplasmosis and toxoplasmosis have been shown to cause monocytosis in as little as 8 to 12 hours after infection. A mild increase in circulating monocytes may also be secondary to a stress leukogram.

Persistent eosinophilia usually indicates a systemic hypersensitivity reaction. Causes include systemic parasitic infections (heartworm infections, migrating parasitic larvae), systemic mastocytosis, allergic reactions, feline asthma, and allergic gastroenteritis. In addition to mastocytosis, some other neoplastic diseases, most notably lymphoproliferative disorders, may be associated with systemic hypersensitivity reactions and persistent eosinophilia.

A persistent eosinophilia is also a feature of hypoadrenocorticism (Addison's disease). In this circumstance there is generally a lymphocytosis and a lack of a mature neutrophilia. Patients with Addison's disease may arrive in a state of collapse or severe weakness and depression. In these instances, a complete blood count is always warranted.

Other lymphocyte responses can also be quite informative in patients with inflammatory disease. Mild to moderate lymphopenia (counts from 750 to 1500 cells/μl) is usually the result of high circulating corticosteroids (stress response). Marked lymphopenia may be caused by stress alone, but other causes of lymphopenia should also be considered. These include any disease state that interferes with the normal circulatory pattern of lymphocytes (lymph to blood to tissues to lymph). Possibilities include lymphoma, chylous effusions, and lymphedema. Chylous effusions and lymphedema are generally characterized by low plasma and serum protein levels.

White blood cell morphology can be as informative in patients with inflammatory conditions as white blood cell numbers.[1-3] Neutrophils should be assessed for toxicity. The most common feature of toxicity in neutrophils is foamy basophilia of the cytoplasm (Color Plate 122-3). Dohle bodies, or intracytoplasmic basophilic precipitates of ribonucleic acid (RNA) (Color Plate 122-4), also represent toxic change. The presence of Dohle bodies indicates significant toxicity in dogs but is far less important in cats, in which they can be seen even in healthy animals. Other features of toxicity include the presence of giant neutrophils and aberrant nuclear shapes such as ring forms.

Table 122-1 General Patterns of Leukocyte Responses

Condition	WBC	Seg	Band	Lymph	Mono	Eos
Acute inflammation	Increased	Increased	Increased	Decreased or no change	Variable	Variable
Chronic inflammation	Increased or no change	Increased or no change	Increased or no change	Increased or no change	Increased	Variable
Overwhelming inflammation	Decreased or no change	Decreased or no change	Increased	Decreased or no change	Variable	Variable
Excitement leukocytosis	Increased	Increased in dogs; increased or no change in cats	No change	No change in dogs; increased in cats	No change	No change
Stress leukogram	Increased	Increased	No change	Decreased	Increased or no change	Decreased or no change

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Eos, Eosinophils; *Mono,* monocytes; *Seg,* segmented neutrophils; *WBC,* white blood cells.

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Neutrophil toxicity indicates that circulating toxins are interfering with neutrophil development in the bone marrow or that neutrophil production has been accelerated in the bone marrow as a result of increased peripheral demand. Toxicity is most commonly associated with bacterial infections but can be observed in other inflammatory diseases as well. For example, toxicity can be seen following extensive tissue necrosis (as sometimes is seen with severe trauma).

Following the appearance and disappearance of neutrophil toxicity can be important for the treatment of the critically ill patients. The appearance of toxicity may indicate that the patient's condition is worsening. Resolution of toxicity is often an indicator of improvement. However, the assessment of toxicity may be prone to subjective evaluation unless the same person reviews the slide daily, making interpretation of changes over time more challenging.

The presence of reactive lymphocytes should also be noted. Reactive lymphocytes are generally larger than normal, with increased amounts of basophilic cytoplasm and large nuclei containing finely granular chromatin. Reactive lymphocytes are antigen stimulated and indicate that the immune system has been engaged.[1-3]

Monocytes and neutrophils should be examined closely for inclusions. A variety of infectious disease agents, including *Ehrlichia, Histoplasma, Hepatozoon,* and *Leishmania,* can sometimes be observed in circulating phagocytes. Erythrophagocytosis is sometimes seen with certain red blood cell disorders such as immune-mediated hemolytic anemia (IMHA).

122.6 RED BLOOD CELL RESPONSES

Anemia is a common problem in emergent and critically ill patients and may be the sole reason the animal is presented to the veterinarian (see Chapter 120, Anemia). The anemia may be either a primary disease or a secondary accompaniment to some other condition. Blood film evaluation is a critical first step in determining which circumstance exists. The approach to evaluating blood films in anemic animals is summarized in Figure 122-1 and explained in greater detail in the paragraphs that follow.[1-3]

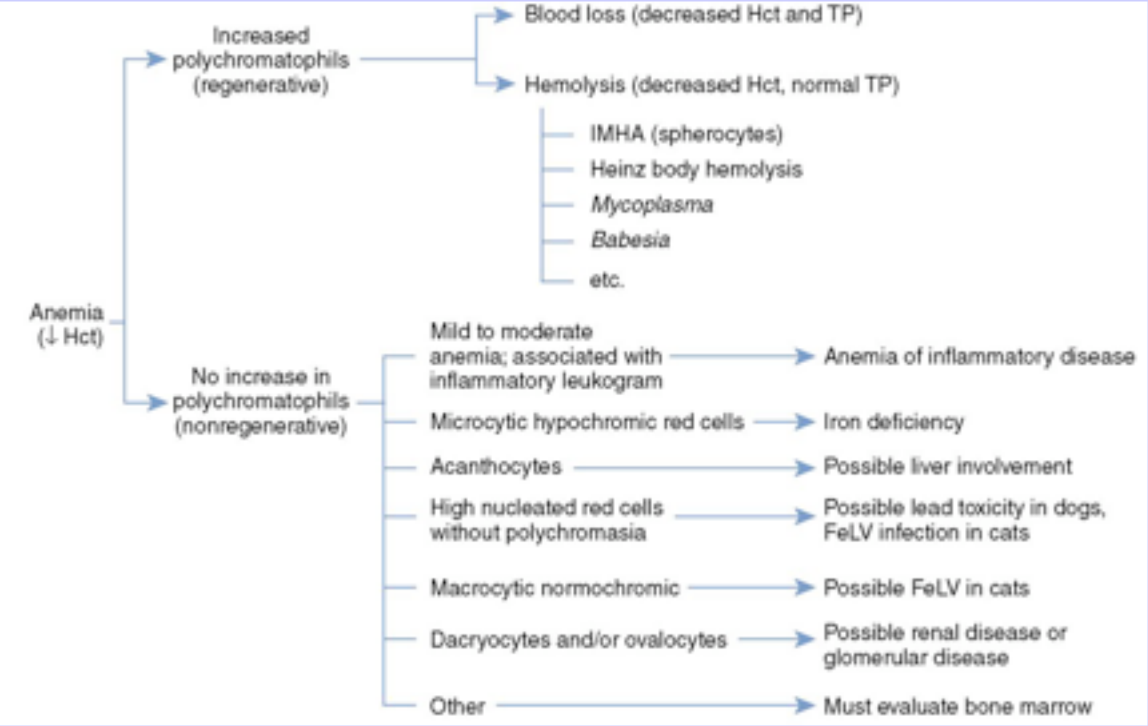
Increased numbers of polychromatophils (large immature red blood cells that are bluish) on the blood film indicate that the anemia is regenerative and the result of either blood loss or hemolysis (see Color Plates 122-1 and 122-2). Blood-loss anemia can usually be easily ruled in or out based upon clinical findings, history, and the total protein concentration (decreased with blood loss).

If there is no indication of blood loss and large numbers of polychromatophils are present, then hemolysis should be considered. Careful evaluation of red blood cell morphology may lead to a specific diagnosis in many cases of hemolysis.

For example, spherocytes are red blood cells that are small, stain intensely, and lack central pallor.[1-3] When large numbers of spherocytes are seen (see Color Plates 122-1 and 122-2), IMHA is the likely diagnosis. Heinz body hemolytic anemia is diagnosed based on finding Heinz bodies, which are single to multiple noselike projections from the red blood cell surface that stain like hemoglobin (Color Plate 122-5).[1-3] In patients with fragmentation hemolytic anemias, large numbers of schizocytes (red blood cell fragments) are usually found on the blood film (Color Plate 122-6).[1-3] In many cases of infectious hemolytic anemia, the causative disease agents can be observed in affected red blood cells. *Mycoplasma* infections are characterized by the presence of small (1 μm) basophilic bodies arranged singly or in chains on the red blood cell surface (Color Plate 122-7).[2,3] In cases of babesiosis, parasitized red blood cells containing teardrop-shaped *Babesia* (2 to 4 μm) can often be found.[2,3]

When polychromasia is absent, the anemia is nonregenerative. Although most types of nonregenerative anemias require bone marrow evaluation for specific diagnosis, some assumptions can be made based on blood film evaluation. When mild to moderate normocytic, normochromic nonregenerative anemias (down to hematocrits of 30% in dogs and 25% in cats) occur in conjunction with an inflammatory leukogram, the anemia is almost certainly the anemia of inflammatory disease. The nonregenerative anemia of iron deficiency (severe blood loss) is characterized by small red blood cells with increased areas of central pallor (Color Plate 122-8).[1-3] Iron-deficient red blood cells are also more fragile than normal and, consequently, there are usually more red blood cell fragments (schizocytes). Nonregenerative anemias that have acanthocytes (red blood cells with 2 to 10 elongated, blunt, fingerlike surface projections) on the blood film are suggestive of liver disease.[1-3] Cases of nonregenerative anemia
that lack polychromasia but have increased nucleated red blood cells (more than 10 per 100 white blood cells 530
counted) most likely result from marrow stromal damage. In dogs this is most likely the result of lead poisoning, 531
whereas in cats feline leukemia virus (FeLV) should be considered (Color Plate 122-9). In cats, nonregenerative anemias with macrocytic normochromic red blood cells also are suggestive of feline leukemia virus infection. Some of these patients may even have megaloblasts (giant fully hemoglobinized red blood cells containing relatively immature, stippled nuclei) on the blood film. Finally, nonregenerative anemias with dacryocytes (tear drop–shaped erythrocytes) or ovalocytes, or both, raise the possibility of myelofibrosis or renal disease (glomerulonephritis) (Color Plate 122-10).

Figure 122-1 Evaluating blood films in anemic patients. *FeLV,* Feline leukemia virus; *Hct,* hematocrit; *IMHA,* immune-mediated hemolytic anemia; *TP,* total protein.



122.7 PLATELET RESPONSES

Platelet numbers should be monitored closely in emergent and critically ill patients[3] (see Chapter 119, Thrombocytopenia). Thrombocytopenia is the most common cause of primary bleeding disorders in dogs and cats. Platelet counts can be estimated rapidly by evaluating the blood film. Normally, there are 8 to 15 platelets per 100× oil immersion monolayer field. This correlates with circulating platelet numbers between 200,000 and 800,000 cells/μl. Certain breeds may have lower platelet counts normally (i.e., Cavalier King Charles Spaniel and Greyhound).

Thrombocytopenia can be a life-threatening event, especially when platelet counts drop below 20,000 to 50,000 cells/μl. Affected animals may have petechiae, ecchymoses, and anemia.

Thrombocytopenia occurs via four mechanisms: sequestration, consumption (utilization), destruction, and hypoproliferation (lack of production) (Table 122-2). Sequestration thrombocytopenia occurs in association with splenomegaly and is extremely rare in animals. Consumption thrombocytopenia is associated with severe inflammation and leads to disseminated intravascular coagulation (DIC). Whenever inflammation is indicated by the leukogram and platelet numbers are even marginally reduced, the possibility of DIC should be considered. In dogs, schizocytes may also be present on the blood film with DIC.

Table 122-2 Causes of Thrombocytopenia

Type	Disorder	Cause
Platelet production defect	Aplasia, hypoplasia	Cytotoxic drugs Idiopathic
	Marrow infiltration (myelophthisis)	Drugs, infection including viral infections
	Ineffective megakaryocytopoiesis	Myelodysplastic syndrome
Accelerated platelet destruction	Immune destruction	Autoantibodies Antibodies to drugs, infection
Peripheral platelet utilization	Nonimmunologic removal	DIC, vasculitis, severe bleeding, neoplasia, infection
Platelet sequestration	Hypersplenism	Enlarged spleen from numerous causes

Modified with permission from Rebar AH, MacWilliams PS, Feldman BF, et al: *A guide to hematology in dogs and cats,* Jackson Hole, WY, 2002, Teton NewMedia.

DIC, Disseminated intravascular coagulation.

Immune-mediated thrombocytopenia (ITP) occurs as the result of antibody-mediated destruction of circulating platelets. Platelet counts may be extremely low and, as a result, platelets on blood films are often quite rare. Bone marrow evaluation reveals increased numbers of platelet precursors (megakaryocytes). 531

532 Destruction thrombocytopenia may occur in conjunction with IMHA, so blood films in suspect cases should be evaluated carefully for evidence of spherocytosis. If seen, a direct antiglobulin test (Coombs' test) is warranted. Patients with combined IMHA and ITP have a more guarded prognosis and are more difficult to treat than those with either IMHA or ITP alone.

Hypoproliferative thrombocytopenia occurs when the marrow is incapable of producing platelets. As in ITP, platelet counts can be extremely low. Marrow evaluation reveals a marked reduction in megakaryocytes.

Hypoproliferative thrombocytopenia may occur alone or in conjunction with other cytopenias (e.g., neutropenia, anemia). Although the specific cause of this syndrome is often obscure, hypoproliferative thrombocytopenia may be caused by certain infections (viruses, *Ehrlichia*) or toxins. It may also be the result of immune-mediated bone marrow disease (antibodies directed against platelet precursors). It is likely that the hypoproliferative thrombocytopenia seen with certain infectious agents is at least partially the result of an immune reaction.

122.8 LEUKEMIA (MYELOID AND LYMPHOID)

Myeloid and lymphoid leukemias are important diseases that often present for medical attention as emergency situations that require close monitoring and critical care. Blood film examination is a critical first step in the diagnosis and evaluation of these conditions. Because patients are presented in various stages of their disease, hematologic findings can vary greatly from case to case.[1]

Perhaps the most consistent finding is a marked nonregenerative anemia. This anemia develops because bone marrow space has been infiltrated by a proliferating neoplastic cell population that is crowding out and interfering with precursors normal red blood cell precursors production. The number of normal circulating leukocytes and platelets is also often decreased.

White blood cell counts may be markedly elevated, normal, or decreased. When white blood cell counts are markedly elevated, it is usually as a result of large numbers of circulating neoplastic cells. In the case of lymphoid leukemias, these cells are usually malignant lymphoblasts, larger-than-normal lymphoid cells with increased amounts of basophilic cytoplasm and large round nuclei containing loose granular chromatin and nucleolar whorls (Color Plate 122-11). Rarely, blood films from patients with lymphoid leukemia have massively increased numbers of neoplastic, but normal-appearing, small lymphocytes. In the case of myelogenous leukemias, the increase in circulating numbers may be due to the predominance of blasts and progranulocytes (acute leukemia) (Color Plate 122-12) or to the presence of more differentiated, but still abnormal, myelocytes, bands, and segmenters (chronic leukemia). Special stains may be needed to differentiate acute myelogenous leukemia from lymphoblastic leukemia.

When white blood cell counts are normal, neoplastic cells may or may not be seen on the blood film. If present, they are usually seen only in low numbers. Leukemias with only rare malignant cells in circulation are sometimes called *subleukemic leukemia*. Cases with this clinical presentation require bone marrow evaluation for definitive diagnosis. Bone marrow aspirates will generally reveal replacement of normal marrow cellular elements by a relatively monotonous population of malignant cells.

When white blood cell counts are low, there is usually no left shift (unless a secondary infection is present), and red blood cell counts are also almost always extremely low without evidence of regeneration. Platelet counts are less predictable. The presence of one or more unexplained cytopenia suggests bone marrow disease and is an indication for bone marrow evaluation. Bone marrow aspirates once again reveal replacement of bone marrow elements by a monotonous population of malignant cells, more than 30% of which are blasts. Leukemias in this stage are termed *myelophthisic syndromes* or *aleukemic leukemias*.

122.9 Suggested Further Reading*

JW Harvey: In *Atlas of veterinary hematology, blood and bone marrow of domestic animals*. 2001, Saunders, Philadelphia, *The most comprehensive veterinary hematology atlas available. Has a large number of excellent illustrations and an extensive reference list, as well as a particularly noteworthy discussion of bone marrow findings*.

AH Rebar: In *Hemogram interpretation for dogs and cats*. 1998, The Gloyd Group, Ralston Purina Handbook Series, St. Louis, *A general overview for systematically interpreting hemogram changes in dogs and cats. Although not focused specifically in the area of emergency and critical care medicine, provides the basic tools for blood film evaluation*.

AH Rebar, PS MacWilliams, BF Feldman, et al.: In *A guide to hematology in dogs and cats*. 2002, Teton NewMedia, Jackson Hole, WY, *A laboratory guide to be used while looking through the microscope. Excellent illustrations of blood films from various disease states in this as in the other two texts. Particularly easy to use because of the bulleted format*.

* See the CD-ROM for a complete list of references

123 Chapter 123 Acute Abdominal Pain

Kenneth J. Drobatz, DVM, MSCE, DACVIM, DACVECC

123.1 KEY POINTS

- The principles of emergency and critical care should be applied initially to any patient with a painful abdomen (stabilize respiratory and cardiovascular systems).
- Any portion of the abdomen or lumbar and sacral spine could be a source of apparent abdominal pain.
- The general causes of abdominal pain include distention of a hollow viscus or organ capsule, ischemia, traction, and inflammation secondary to variety of causes.
- If the underlying cause of abdominal pain can be identified quickly and treated, the occurrence of more serious complications such as septic peritonitis or systemic inflammatory response syndrome and multiorgan dysfunction syndrome can be minimized.

123.2 INTRODUCTION

Animals with an acute condition of the abdomen are characterized primarily as having abdominal pain. Vomiting and/or diarrhea often accompany this abdominal pain as well. As with any patient with an emergent condition, the basic principles of stabilization of the four most important body systems (respiratory, cardiovascular, neurologic, and renal systems) should be applied when initially assessing and stabilizing these patients.

After initial stabilization, a thorough diagnostic evaluation should be performed to determine the underlying cause as soon as possible so that definitive care can be provided. The general causes of abdominal pain include distention of a hollow viscus or organ capsule, ischemia, traction, and inflammation secondary to variety of causes. If left untreated, any of these causes could result in necrosis of tissue and loss of function; therefore it is imperative that the underlying cause be identified quickly. Prompt identification and treatment of the underlying abnormality will minimize the occurrence of more serious complications such as septic peritonitis or systemic inflammatory response syndrome and multiorgan dysfunction syndrome.

123.3 DIAGNOSTIC EVALUATION

The diagnostic evaluation of animals with abdominal pain begins with signalment, medical history, and physical examination, followed by blood work, radiographs, abdominal ultrasound, radiographic contrast studies, abdominocentesis, peritoneal lavage, response to treatment, and/or exploratory laparotomy. The list of specific causes of abdominal pain is extensive, because any portion of the abdomen could be a source of pain. Intervertebral disk disease may also simulate a painful abdomen, but direct palpation of the area of spinal pain will usually elicit a more diagnostic response.

123.3.1 Signalment and History

Signalment can be a clue to the cause of abdominal pain or vomiting. For example, young animals commonly swallow foreign bodies or contract infectious diseases. An older, intact male dog may have a painful prostate.

Abdominal pain in an intact female dog with a pyometra should raise concern of a possible uterine rupture and septic peritonitis. Young adult German Shepherd dogs with pancreatic exocrine insufficiency are predisposed to mesenteric volvulus. String foreign bodies are common in cats. Acute pancreatitis commonly occurs in middle-aged, obese female dogs.

An accurate history may be the most important diagnostic clue in the assessment of animals with acute abdominal pain. Questions should include the potential for exposure to toxins or dietary indiscretion. Additionally, is ingestion of a foreign body a possibility? Are any other animals affected? Has the animal had any major medical problems in the past? Is the patient currently receiving any medications, including over-the-counter drugs such as aspirin or other nonsteroidal antiinflammatory medications? Is there a possibility of trauma? Could the patient have been exposed to any other animals? Is the patient current on all vaccinations? The clinician should determine when the animal's condition was last normal, what the first abnormal sign was, and the progression of clinical signs since the problem began.

The progression of the clinical signs can also help determine the urgency of diagnosing the underlying cause. Chronic abdominal pain that has remained relatively static in its progression is not usually an emergency, although the problem could become an emergency at some point. An animal that has a chronic problem and has deteriorated rapidly or an animal with an acute problem that is or is not deteriorating rapidly warrants a more aggressive and expedient approach to define the underlying cause of the painful abdomen.

123.3.2

Physical Examination

A full physical examination should be performed, with initial attention given to the cardiovascular, respiratory, central nervous, and renal systems, as for any critically ill patient. More specifically for the animal with acute abdominal pain, a careful and detailed abdominal palpation may occasionally locate the specific area of pain, (a loop of intestine, the prostate, or the kidneys) and this may help in the diagnostic approach. Many times, a specific area cannot be identified and diagnosing the underlying cause requires assimilation of information from a variety of diagnostic tests; these include clinical pathology, abdominal imaging, abdominocentesis, diagnostic peritoneal lavage, response to treatment, and/or exploratory laparotomy.

123.3.3

Emergency Clinical Pathology

An extended database that includes a packed cell volume (PCV), total solids (TS), glucose, dipstick blood urea nitrogen (BUN), blood smear, venous blood gas, and electrolyte levels (including sodium, potassium, chloride, and ionized calcium) helps in rapidly providing a relatively well-rounded metabolic assessment of the patient and can sometimes point toward the underlying cause.

The PCV and TS should always be assessed together. Parallel increases in both suggest dehydration. A normal or increased PCV with a normal to low TS indicates protein loss from the vasculature. In animals with an acute condition of the abdomen, this clinicopathologic picture is often associated with protein loss from peritonitis. Hemorrhagic gastroenteritis (HGE) is associated with a very high PCV (60% to 90%) and normal or low TS. A dog with an acute onset of vomiting and bloody diarrhea and these changes in PCV and TS make HE the most likely diagnosis.

Hemorrhage most commonly results in a parallel decrease in the PCV and TS, although in animals with acute hemorrhage these changes may not initially be recognized until intravenous fluid therapy has been provided. Acute hemorrhage in dogs can sometimes be recognized by a normal or increased PCV and normal or decreased TS. Splenic contraction in dogs makes TS a more sensitive indicator of acute blood loss than PCV. The most common causes of acute hemorrhage in dogs with acute conditions of the abdomen are splenic rupture (usually secondary to neoplasia) and severe hemorrhage from gastrointestinal (GI) ulceration. In cats with an acute condition of the abdomen, the most common cause of acute hemorrhage is abdominal hemorrhage secondary to hepatic neoplasia.[1]

Blood glucose measurement is easily and rapidly obtained by dipstick methods and a glucometer. Increased blood glucose in a dog with an acute condition of the abdomen may be associated with diabetes or transient diabetes associated with severe pancreatitis. Blood glucose is rarely quite high in dogs with extreme hypovolemia secondary to severe abdominal or GI hemorrhage, presumably a result of the effects of catecholamines on glycogenolysis and gluconeogenesis. Physical examination findings of extremely poor tissue perfusion are evident, and it is clear that the animal may die imminently if the hypovolemia is not corrected rapidly. Increased blood glucose levels in cats may be associated with stress or diabetes. Hyperglycemia in cats is not as useful diagnostically as it is in dogs.

Decreased blood glucose is often associated with sepsis and warrants an aggressive approach to find the underlying cause of the acute abdominal pain, particularly if septic peritonitis might be present. Rarely, extremely low blood glucose levels may occur as a result of sepsis, but more typically it falls in the 40 to 60 mg/dl range. Hypoadrenocorticism may also be a cause of low blood glucose levels.

Dipstick BUN provides an estimate of azotemia in an animal with an acute condition of the abdomen. Increased BUN may be due to prerenal, renal, or postrenal causes. Increased BUN may also be noted in animals with acute abdominal pain caused by pyelonephritis or ureteral or urethral obstruction. Disproportionately high BUN compared with creatinine levels should prompt the clinician to rule out GI hemorrhage.

Reliable assessment of a blood smear depends on a good-quality sample. All cell lines should be evaluated systematically, including the red blood cells, white blood cells, and platelets. The average number of platelets per monolayer field under oil immersion should be estimated (see Chapter 122, Blood Film Evaluation). The smear should first be screened at low power to search for platelet clumps that may result in a falsely low platelet estimate before evaluating the counting area under oil immersion. In normal dogs and cats, there are 8 to 15 platelets per oil immersion field; each platelet in a monolayer field is equivalent to approximately 15,000 platelets/μl. If there are more than 4 to 5 platelets per field, it is unlikely that the bleeding is strictly due to thrombocytopenia. Most patients with spontaneous bleeding due to thrombocytopenia have less than 2 platelets per oil immersion field. A decreased number of platelets is one of the most consistent findings in animals with disseminated intravascular coagulation (DIC). Animals with acute conditions of the abdomen may have DIC secondary to systemic inflammation or massive peritoneal inflammation.

Red blood cell morphology should be examined. Anisocytosis, macrocytosis, and polychromasia indicate regeneration. Schistocytes or fragments of red blood cells suggest DIC. Heinz bodies are often seen in systemically ill cats. The smear should be scanned at lower power to get an estimate of the number of white blood cells and then at higher power to assess the character of the white blood cells. Leukocytosis with a mature neutrophilia suggests an inflammatory or infectious process. Band cells indicate a more severe inflammatory or infectious process. The absence of a leukocytosis or a left shift does not rule out an inflammatory or infectious process. Leukopenia can be due to decreased production or sequestration of white blood cells, a viral infection such as parvovirus, or immunosuppressive drugs.

A venous blood gas provides an evaluation of the metabolic acid-base status. Animals that have severe vomiting due to GI foreign bodies may have a hypochloremic metabolic alkalosis as well as hypokalemia and hyponatremia.[2] Often, a metabolic acidosis is also present due to severe diarrhea or lactic acidosis from hypoperfusion.[2]

123.3.4 Abdominal Radiographs

A full description of all radiographic and ultrasonographic findings in an animal with acute abdominal pain is beyond the scope of this chapter, but specific points regarding plain abdominal radiographs are provided. Abdominal radiographs should be obtained in any animal with abdominal pain. A systematic and detailed review of all abdominal and extraabdominal structures should be performed. All organs in the abdominal cavity should be evaluated for density, shape, size, and location. Abnormalities in any organ may help localize the cause of the abdominal pain. Extraabdominal structures should be examined for completeness of evaluation and further diagnostic clues. The retroperitoneal space should be assessed as well. Loss of detail of the kidneys, a “streaky” appearance, or distention of the retroperitoneal space suggests fluid accumulation, a space-occupying mass, or sublumbar lymphadenopathy. The structures that make up the abdominal compartment “walls” should be carefully assessed for integrity to rule out herniation or rupture.

Evidence of free gas in the peritoneum without prior abdominocentesis or recent abdominal surgery suggests intestinal perforation or the presence of gas-forming organisms within the abdominal cavity. Free gas is detected 535
most commonly between the stomach or liver and the diaphragm on the lateral radiograph. A horizontal beam 536
radiograph with the animal in left lateral recumbency and focused at the least dependent area can increase the sensitivity for identifying free gas in the peritoneal space. A large volume of free gas in the peritoneal is often associated with pneumocystography of a ruptured urinary bladder, a ruptured vagina, post abdominal surgery, ruptured gastric dilatation-volvulus, pneumoperitoneography, or extension of a pneumomediastinum. Pneumomediastinum is most often associated with pneumoretroperitoneum, although on rare occasions, pneumoperitoneum can occur. A small volume of free gas in the peritoneal space is associated most often with rupture of the GI tract or infection with a gas-forming organism. Gas in the spleen or liver is most often associated with a clostridia infection.

Segmental gaseous or fluid distention of the small bowel suggests an intestinal obstruction. The normal diameter of the small intestine in the dog is approximately 2 to 3 times the width of a rib, or less than the width of an intercostal space. Additionally, all of the small bowel loops should have a similar diameter, and it is abnormal for one segment to be 50% larger than other portions. Feline small intestines should not exceed twice the height of the central portion of L4 vertebral body, or 12 mm.[3]

Generalized small bowel distention suggests generalized small bowel ileus or a very low GI obstruction. Localized small bowel distention is not always a definitive finding for intestinal obstruction but should prompt further investigation if an obvious foreign body is not evident. One option is to repeat plain radiographs 3 hours later. If the bowel remains distended in the same area, this suggests a bowel obstruction. A more definitive diagnosis for intestinal obstruction can be obtained by an upper GI positive contrast study with barium. Severe intraperitoneal inflammation and granuloma formation can occur if barium leakage occurs as a result of a bowel rupture. This problem can be minimized if abdominal surgery with peritoneal lavage is done immediately, as indicated after the diagnosis of small bowel rupture. Therefore upper GI contrast study with barium is not contraindicated if one is attempting to diagnose GI perforation.

Loss of abdominal detail on plain abdominal radiographs may be due to lack of fat in the abdomen (puppies or very thin animals), free abdominal fluid, pancreatitis, large mass(es), or carcinomatosis.

123.3.5 Abdominal Fluid Analysis

It is important to obtain free abdominal fluid for analysis if it is present in an animal with a painful abdomen. Abdominal fluid analysis can help rule out septic peritonitis and may also provide a diagnosis or help direct further diagnostic investigation. Fluid may be obtained by abdominocentesis (blindly or by ultrasound guidance). If fluid cannot be obtained but is still suspected to be present, a diagnostic peritoneal lavage is indicated (see Chapter 156, Diagnostic Peritoneal Lavage).

Free abdominal fluid should be analyzed for creatinine and/or potassium, and compared with peripheral blood concentrations if urinary tract leakage is suspected. Creatinine and potassium will be higher in the abdominal fluid if a uroperitoneum is present.[4,5] Measurement of fluid glucose and lactate concentrations may be helpful in diagnosing a bacterial peritonitis. These measurements can be compared with simultaneously collected peripheral blood glucose and lactate concentrations. A glucose gradient greater than 20 mg/dl of peripheral blood to abdominal fluid was 100% sensitive and 100% specific in diagnosing septic peritonitis in dogs (86% sensitive and 100% specific in cats) in one study. Additionally, a blood-to-abdominal fluid lactate gradient of 2 mmol/L or more was also 100% sensitive and 100% specific in diagnosing septic peritonitis in dogs.[6] If bile peritonitis is suspected, abdominal bilirubin concentration will often be higher than simultaneously collected blood bilirubin concentration.[7]

A pure transudate is grossly clear and is characterized by a total protein less than 2.5 g/dl and low cell count (<500 cells/µl). Of the few cells present, most are either nondegenerate neutrophils or reactive mesothelial cells. The most common causes of a pure transudate in the abdomen include hypoalbuminemia and portal venous obstruction.

A modified transudate is usually serous to serosanguineous, with a total protein level between 2.5 and 5 g/dl and a moderate total cell count (300 to 5500 cells/µl). Depending on the cause, there may be variable numbers of red blood cells, nondegenerate neutrophils, mesothelial cells, macrophages, and lymphocytes. This type of effusion is often due to passive congestion of the liver and viscera and impaired drainage of the lymphatic vessels. The most common causes include right-sided heart failure, dirofilariasis, neoplasia, and liver disease.

An exudate is often cloudy, and has a total protein concentration greater than 3 g/dl and a cell count greater than 5000 to 7000 cells/µl. The predominant cell type is the neutrophil, although numerous other cells may be present as well. This is the most common type of free abdominal fluid associated with acute abdominal pain. Exudates can be septic or nonseptic, but making this classification can be challenging at times. Septic exudates are characterized by the presence of intracellular and extracellular bacteria. In most animals with septic peritonitis, cytologic evidence of bacteria can be found, particularly if one has patience and explores numerous microscopic fields and also examines the cytology of the sediment of the abdominal fluid. Rarely, septic peritonitis can be present despite the absence of cytologic evidence of bacteria in the fluid.

123.4 SURGICAL VERSUS MEDICAL MANAGEMENT

One of the most challenging decisions regarding animals with acute abdominal pain is deciding whether immediate surgery is indicated. Clear indications for immediate surgery include abdominal wall perforation, septic peritonitis, persistent abdominal hemorrhage, intestinal obstruction, intestinal foreign body causing pain or bowel obstruction, uroperitoneum, free abdominal gas (not associated with previous surgery, pneumomediastinum, or invasive procedures), abdominal abscess, ischemic bowel, gastric dilation volvulus, mesenteric volvulus, and bile peritonitis.

Without these clear indications, the clinician must use all information that can be obtained quickly to determine if exploratory surgery is warranted, including signalment, history, physical examination, clinicopathology, imaging modalities, response to medical therapy, informed discussion with the owner, and clinical intuition. Using all this information, the correct decision of whether to perform exploratory surgery or not is usually made.

123.5 SUGGESTED FURTHER READING*

AK Boag, RJ Coe, TA Martinez, D Hughes: Acid-base and electrolyte abnormalities in dogs with gastrointestinal foreign bodies. *J Vet Intern Med*. **19**, 2005, 816, *An excellent data-based paper evaluating blood gas and electrolyte changes in dogs with intestinal foreign bodies.*

D Mandell, KJ Drobatz: Feline hemoperitoneum, a retrospective study. *J Vet Emerg Crit Care*. **5**, 1995, 93, *The only data-based study on hemoperitoneum in the cat.*

JM Owens, DN Biery: In *Radiographic interpretation for the small animal clinician*. ed 2, 1999, Williams & Wilkins, Media, PA, *An outline-based summary of the radiographic interpretation of small animal radiographs; easy to use and very clinically oriented.*

* See the CD-ROM for a complete list of references

124 Chapter 124 Acute Pancreatitis

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124.1 KEY POINTS

- Acute pancreatitis is an inflammatory disease, with episodes ranging in severity from mild and self-limiting to severe fulminant disease with extensive necrosis, systemic inflammation, and multiorgan failure.
- Clinical signs, physical examination findings, and results of diagnostic evaluation are variable and often nonspecific in dogs and cats with AP.
- Suggested risk factors associated with increased morbidity and mortality include older age, obesity, gastrointestinal disease, and concurrent endocrinopathies in dogs, and ionized hypocalcemia in cats. Hepatic lipidosis and other concurrent diseases are also associated with more severe disease in cats.
- Evaluation of serum amylase and lipase concentrations is not useful for diagnosis of AP in dogs and cats.
- Early, aggressive intravascular volume resuscitation and intensive monitoring are crucial for patients with severe acute pancreatitis.
- Early enteral nutrition and aggressive pain control are important aspects of therapy, whereas prophylactic antibiotic therapy and surgical intervention are indicated infrequently.
- There is a great need for development of consensus definitions, prognostic scoring systems, and other objective means of determining and stratifying severity of AP in veterinary patients.

124.2 INTRODUCTION

Pancreatitis, broadly classified as acute, recurrent, or chronic, is a fairly common disease in dogs and is becoming more widely recognized in cats. [1,2] Acute and recurrent acute pancreatitis (AP) are characterized by episodes of pancreatic inflammation with a sudden onset and variable course. Episodes may range in severity from mild and self-limiting to severe fulminant disease with extensive necrosis, systemic inflammation and/or sepsis, multiorgan failure, and death. In addition to these systemic complications, severe acute pancreatitis (SAP) (may include local complications such as pancreatic necrosis, pancreatic pseudocysts, and pancreatic abscesses.[3] In veterinary medicine there is no universally accepted classification scheme for pancreatitis, with most current schemes based on variable terminology and histopathologic descriptions. However, these usually are not available at the time of diagnosis and do not necessarily correlate well with clinical severity and disease progression.[3–5] Therefore a clinically based classification system, simplified and adapted from consensus definitions in human medicine[3]and recently used by other authors,[1,2,6] may be more appropriate to our patient population and is used in this chapter.

124.3 PATHOPHYSIOLOGY

A number of factors have been implicated as potential etiologic factors of pancreatitis. In humans, most cases of AP are caused by biliary calculi or alcohol abuse. Most cases in dogs and cats, however, are considered to be idiopathic, because a direct causal relationship is not often demonstrated.* Regardless of the underlying etiology, AP involves intrapancreatic activation of digestive enzymes with resultant pancreatic autodigestion. Studies of animal models suggest that initial events occur within the acinar cell by abnormal fusion of normally segregated lysosomes with zymogen granules (catalytically inactive forms of pancreatic enzymes), resulting in premature activation of trypsinogen to trypsin, and may involve changes in signal transduction and increases in intracellular ionized calcium (iCa) concentrations.[10] Trypsin in turn activates other proenzymes, setting in motion a cascade of local and systemic effects that are responsible for the clinical manifestations of AP.

Local ischemia, phospholipase A_2, and oxygen free radicals (produced in part from activation of xanthine oxidase by chymotrypsin) disrupt cell membranes, leading to pancreatic hemorrhage and necrosis, increased capillary permeability, and initiation of the arachidonic acid cascade. Elastase can cause increased vascular permeability secondary to degradation of elastin in vessel walls. Phospholipase A_2 degrades surfactant, promoting development of pulmonary edema, acute lung injury (ALI), and acute respiratory distress syndrome (ARDS) (see Chapter 24, Acute Lung Injury and Acute Respiratory Distress Syndrome). Trypsin may activate the complement cascade, leading to an influx of inflammatory cells and production of multiple cytokines and more free radicals. Trypsin can also activate the kallikrein-kinin system resulting in vasodilation, hypotension, and possibly acute renal failure, and the coagulation and fibrinolytic pathways, resulting in microvascular thromboses and disseminated intravascular coagulation (DIC). Local inflammation and increases in pancreatic and peripancreatic microvascular permeability may cause massive fluid losses, further compromising perfusion and stimulating additional recruitment of inflammatory cells and mediators, leading to a vicious cycle culminating in the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) (see Chapter 11, Systemic Inflammatory Response Syndrome).

* Interested readers are referred to references 1, 2, 7, and 1, 2, 7–11 for more in-depth reviews of etiologies and pathophysiology, respectively.

124.4 CLINICAL PRESENTATION

Clinical signs and presentation associated with AP are variable and often nonspecific, particularly in cats, and may be difficult to distinguish from those of other acute abdominal disorders. Dogs with AP are usually presented because of anorexia, vomiting, weakness, depression, and sometimes diarrhea.[12,13] They may be febrile, dehydrated, and icteric, and often exhibit signs of abdominal discomfort, sometimes with abdominal distention and absent bowel sounds from associated peritonitis and intestinal ileus. Dogs that are middle-aged and older, those that are overweight, have a history of prior or recurrent gastrointestinal (GI) disturbances, and those with concurrent endocrinopathies (diabetes mellitus [DM], hypothyroidism, or hyperadrenocorticism) have been suggested to be at increased risk for development of fatal SAP.[6,13,14] Yorkshire Terriers, Miniature Schnauzers, and other terrier breeds may also be at increased risk.[13,14] Common clinical findings in cats with AP include lethargy, anorexia, dehydration, and hypothermia; vomiting and abdominal pain appear to be reported less frequently.[15-17] Icterus and pallor often are noted as well.[4,17] Concurrent conditions such as hepatic lipidosis, inflammatory bowel disease (IBD), interstitial nephritis, DM, and cholangitis-cholangiohepatitis occur frequently, and signs of these conditions may predominate.[1,5,15-17] In either species, patients with SAP may present with signs of systemic complications including dyspnea, bleeding disorders, cardiac arrhythmias, oliguria, shock, and collapse.

124.5 DIAGNOSIS

Diagnosis of AP requires careful integration of historical, physical examination, laboratory, and diagnostic imaging findings combined with a high degree of suspicion. Because many of these findings may be nonspecific and there is wide variation in disease severity, diagnosis can be challenging. Clinicians should keep in mind that the absence of specific findings in any one diagnostic test does not rule out the possibility of AP.

124.5.1 Laboratory Assessment

Initial hemogram and serum chemistry profile abnormalities are variable and nonspecific, and may reflect concurrent extrapancreatic disease. Neutrophilic leukocytosis with a left shift is most commonly reported,[1,12,15] although neutropenia has also been reported in dogs.[12] Thrombocytopenia also appears to be common.[12] The hematocrit and red blood cell counts may be normal, although anemia may also be seen, especially in cats.[15,16] An elevated hematocrit reflecting hemoconcentration and dehydration may be present; in human patients with AP this is associated with more severe disease. Elevations in hepatic enzyme activities and total bilirubin are often noted,[5,12,15,16] which may reflect ischemic and/or toxic hepatocellular injury or concurrent hepatobiliary disease. Patients are frequently azotemic, usually from prerenal causes, although acute renal failure may also be present.[12,14,15] Hyperglycemia is common[6,12,15] and is thought to be secondary to stress-related increases in endogenous cortisol and catecholamine levels, to hyperglucagonemia, or to overt DM. However, hypoglycemia may be seen if concurrent hepatic dysfunction, SIRS, or sepsis is present. Hypercalcemia has been reported in some dogs with SAP.[12] Mild to moderate hypocalcemia and hypomagnesemia are not uncommon, possibly as a result of pancreatic and peripancreatic fat saponification, although multiple mechanisms have been proposed.[17,18] Ionized hypocalcemia appears to be common in cats with AP and is associated with a poorer outcome.[17] Other common findings include hypoalbuminemia secondary to GI losses, sequestration, and shifting of protein production to acute phase proteins, hypokalemia, hypercholesterolemia, and hypertriglyceridemia. Hyperlipemia may be grossly apparent and may interfere with determination of other serum chemistry values.[1,2,12,14]

Increased activities of lipase and amylase historically have been used as markers of pancreatitis, but are of limited diagnostic value because elevations may also occur from extrapancreatic sources such as azotemia and glucocorticoid administration.[1,2,12,18] Furthermore, lipase and amylase activities are often within normal limits in animals with confirmed pancreatitis, particularly cats.[1,2,12,15,19]

Elevations in trypsin-like immunoreactivity (TLI) may suggest a diagnosis of pancreatitis, but also occurs with azotemia, and with GI disease in cats[5]; TLI may be normal in some patients with AP.[5,20,21] Although it is neither sensitive nor specific, evaluation of TLI may have some clinical utility in cats in combination with diagnostic imaging,[20] but is not considered useful in dogs.[1,18]

Species-specific pancreatic lipase immunoreactivity (fPLI, cPLI) assays have recently been validated for use in cats and dogs, respectively.[1,18] Initial data suggest that PLI is highly sensitive and specific for AP in experimental and spontaneous cases of AP in both species, and does not appear to be affected by renal disease or glucocorticoid administration.[1,18,21] Furthermore, serial evaluation of PLI may be helpful in monitoring disease progression, at least in dogs.[22]

124.5.2 Diagnostic Imaging

Abdominal radiographs are neither sensitive nor specific for AP but may provide supportive evidence, and are especially valuable in helping to rule out other causes of acute abdominal disease such as intestinal obstruction or perforation. In dogs radiographic signs may include increased density and loss of detail in the right cranial abdomen, displacement of the descending duodenum to the right with widening of the angle between the proximal duodenum and the pylorus, and caudal displacement of the transverse colon. Gastric distention and static gas patterns suggestive of ileus may be noted in the descending duodenum and transverse colon.[1,2,12,18] Abdominal radiographs in cats typically are nonspecific, with decreased peritoneal detail most commonly reported; hepatomegaly, a mass effect in the cranial abdomen, and small intestinal dilation have also been reported.[4,15,16,23]

Abdominal ultrasonography (US) is particularly helpful as a diagnostic tool, for monitoring progression of the disease, and for evaluating the extent of associated complications and concurrent disorders. The pancreas may appear enlarged and hypoechoic, suggesting edema or necrosis, with hyperechoic peripancreatic tissue. More subtle changes such as pancreatic duct dilation, thromboses, and organ infarcts also may be detected.[12,17,21,23,24] In human patients with AP, color Doppler US is the method of choice for detection of vascular complications including thromboses and organ infarcts.[24] US is also valuable for identifying and guiding sampling of masses, localized inflammation, and focal or regional fluid accumulations including pancreatic pseudocysts and abscesses.* US-guided fine-needle aspiration (FNA) of pancreatic necrosis is used routinely in humans with AP to identify infected pancreatic necrosis[26-29] and recently has been described in dogs.[24]

Contrast-enhanced abdominal computed tomography (CT) is considered the gold standard in human patients with AP for identifying pancreatic necrosis and peripancreatic fluid collections.[3,26-28] Preliminary studies in veterinary patients suggested that CT was not particularly sensitive for diagnosis of AP in cats,[20,21] although a more recent study shows promising results.[30] Contrast-enhanced CT has been used to identify pancreatic necrosis in two dogs with AP.[24]

* References 5, 12, 16, 17, 24, 25.

124.5.3 Additional Diagnostic Evaluation

Additional diagnostic evaluation not specific for AP but to help determine patient status and provide baseline information for subsequent monitoring may include urinalysis, urine culture and sensitivity, thoracic radiographs, evaluation of venous and arterial blood gases, lactate and iCa concentrations, and a complete coagulation profile. Coagulation abnormalities reflecting DIC and thromboses appear to be common in dogs and cats with SAP.[6,12,15-17,24] If focal or regional fluid accumulations (including pleural effusions) are detected, these should be sampled, with fluid analysis, cytology, and cultures evaluated as indicated. Serial cytologic evaluation may be helpful in monitoring disease progression. It has also been suggested that detection of amylase and lipase activities in peritoneal or focal fluid accumulations greater than those in serum may suggest a diagnosis of pancreatitis and/or confirm the presence of a pseudocyst.[25]

124.6 DETERMINING SEVERITY

Because of the variability in presentation, early determination of disease severity and identification of those patients at risk for more severe disease would help guide earlier, more aggressive goal-oriented monitoring and therapy. In human medicine, various clinical scoring systems and biochemical markers have been evaluated as objective methods for early determination of severity. In addition to selecting patients for earlier admission to an intensive care unit, these allow objective stratification of patients for prognostic purposes, for evaluating disease progression, and for clinical research including evaluation and comparison of various treatment protocols.

Clinical scoring systems include pancreatitis-specific scoring systems such as Ranson's Criteria, the Glasgow Coma Scale score, and Balthazar's CT index, and more generalized predictors of severity such as the Acute Physiology and Chronic Health Evaluation (APACHE) II and III scores.[†] The clinical classification system mentioned previously[3] includes components of some of these scoring systems.

Of the many biochemical markers evaluated, pancreas-specific ones such as trypsinogen activation peptides (TAP) and carboxypeptidase, and more global markers of systemic inflammation such as C-reactive protein (CRP), interleukin-6, interleukin-8, and neutrophil elastase seem most promising.[‡] CRP is currently the best established and most widely available biochemical marker for predicting severity.

In veterinary medicine, in addition to the potential risk factors previously described, a simplified scoring system based on organ involvement has been proposed for dogs with AP,[34] and a survival prediction index has been developed for critically ill dogs (see Chapter 3, Survival Prediction Index). Increases in CRP[35] and urinary TAP-to-creatinine ratios[6] have been demonstrated in dogs with spontaneous AP, although further evaluation is needed to determine their clinical utility.

[†] For interested readers, these clinical scoring systems are reviewed in detail in references 27 and 31-33.

[‡] For interested readers, more in-depth reviews of biochemical markers are provided in references 9, 27, and 31-33.

124.7 TREATMENT

Therapy for patients with AP involves eliminating any identifiable underlying cause, if possible, symptomatic and supportive therapy, and anticipation of and early aggressive intervention against systemic complications. Although severity scoring systems and prognostic indicators are valuable, these do not replace the need for intensive monitoring and therapy on an individual basis. Patients that initially appear stable can decompensate rapidly, so close monitoring and frequent reassessment is critical. Throughout this section the reader is referred to related chapters in this book for more specific details on various therapies and monitoring.

124.7.1 Resuscitation, Fluid Therapy, and Monitoring

Patients with severe disease may be hemodynamically unstable and in need of rapid resuscitation with shock-rate replacement fluids. Maintenance fluid requirements may also be substantial, to combat massive ongoing fluid losses from the vascular space due to vomiting and third spacing into the peritoneal cavity, GI tract, and the interstitium.

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Balanced electrolyte solutions are appropriate for maintenance needs, but should be modified based on frequent evaluation of electrolyte and acid-base status. Potassium supplementation is usually necessary. Calcium should not be supplemented unless clinical signs of tetany are observed, because of the potential for exacerbation of free radical production and cellular injury. Concurrent use of a synthetic colloid such as hetastarch is usually necessary for patients with severe disease. This will reduce the volume of crystalloids needed, and may help maintain intravascular volume and improve microcirculatory perfusion and oxygen delivery.

Frequent monitoring of vital signs, arterial blood pressure, central venous pressure, and urine output may help guide rates and types of intravenous fluids while avoiding overhydration. Other parameters that require frequent monitoring include hematocrit and total plasma solids; blood glucose, albumin, and lactate; oxygenation and ventilation; an electrocardiogram; coagulation status; renal function; and mentation.

Patients that are hypotensive despite adequate volume replacement will need pressor therapy; dopamine may be used, although in some instances norepinephrine, phenylephrine, or epinephrine may be necessary. In experimental feline models of AP, low-dose dopamine (5 μg/kg/min) has been shown to reduce the degree of pancreatic inflammation by decreasing microvascular permeability,[36] although there have been no controlled studies in cats or dogs with spontaneous disease.

Supplemental oxygen is indicated for patients with evidence of hypovolemic shock and/or respiratory abnormalities. Patients that present with or develop tachypnea or dyspnea should be evaluated for ALI and ARDS, as well as aspiration pneumonia, pleural effusion, pulmonary thromboembolism, overhydration, and preexisting cardiopulmonary disease, and appropriate therapy instituted. Systemic causes of tachypnea such as metabolic acidosis, pain, and hyperthermia should also be considered. Patients with significant anemia may require packed red blood cell transfusions. This may be more of a problem in cats and small dogs, in part as a result of repeated blood sampling.

Use of fresh frozen plasma (FFP) often is advocated for patients with SAP to provide a source of α_2-macroglobulins, important protease inhibitors that help to clear activated circulating proteases. In experimental canine pancreatitis, depletion of α_2-macroglobulins is followed rapidly by DIC, shock, and death.[1,2,7] However, studies in human patients with SAP have not shown any improvement in morbidity or outcome with use of plasma,[37] and there have been no controlled studies in veterinary patients with spontaneous disease. FFP administration is indicated for treatment of coagulopathies including DIC, and anecdotally many clinicians think that FFP is useful in dogs and cats with SAP (although it is unclear if this is because of concurrent coagulopathies).

124.7.2 Pain Management

Aggressive analgesic therapy is indicated for all patients with AP, including those that may not exhibit overt signs of pain. Adequate analgesic therapy is critical for maintaining patient comfort and will help decrease levels of stress hormones, will improve ventilation, and may improve GI motility if ileus is due in part to pain. Systemic opioids are the mainstay of therapy, and may be supplemented with low-dose ketamine or lidocaine, or both, in patients with more severe pain. Low-dose lidocaine has promotility effects and may be particularly beneficial for patients with severe ileus. Epidural and intraperitoneal analgesia may also be effective in select patients. Nonsteroidal antiinflammatory agents are not recommended unless patients are hemodynamically stable, not azotemic, and are well perfused.

124.7.3 Nutrition

A traditional aspect of therapy for AP involves withholding food and water to reduce pancreatic secretions and allow the pancreas time to recover. This is reasonable for mild cases and when there has not been a prolonged period of anorexia; most mild cases of AP resolve after restricting oral intake for 2 to 4 days, followed by gradual reintroduction of water and then small, carbohydrate-rich meals. Patients with SAP, however, are in a hypercatabolic state and for these patients early enteral nutrition is indicated.[1,26-28,38]

Potential benefits of early enteral nutrition in patients with SAP include improved gut mucosal structure and function and decreased bacterial translocation, thus attenuating stimuli for propagation of SIRS.[26,38,39]

Compared with parenteral nutrition, enteral feeding is associated with fewer complications including fewer infections, less expense, and shorter duration of hospitalization.[26,27,38] Use of a jejunostomy tube to deliver nutrients to the jejunum is thought to minimally stimulate exocrine pancreatic secretion; however, it is not clear if exocrine pancreatic function is altered during AP, or whether stimulation of these secretions is actually detrimental. Because jejunostomy tube placement can be technically difficult and usually requires general anesthesia and special equipment, many veterinary clinicians have used other routes of enteral feeding including nasogastric and esophagostomy tubes, particularly in cats with AP because of the risk for hepatic lipidosis.[1,2] Preliminary studies suggest that nasogastric tube feeding in cats[40] and human patients[41] with SAP is well tolerated and feasible. Patients with severe ileus or intractable vomiting may tolerate low-volume enteral nutrition (trickle feeding or microenteral nutrition); however, supplemental total or partial parenteral nutrition should be used when nutritional requirements cannot be met with enteral nutrition alone. Elemental or partial-elemental diets are usually recommended; although the ideal composition is unknown, supplementation with glutamine is currently recommended.[26] Cats, particularly those with concurrent GI tract disease, may require parenteral cobalamin supplementation.[1] Close monitoring for complications associated with refeeding is critical, and overfeeding should be avoided.

124.7.4

Additional and Supportive Therapy

Other therapies that don't necessarily influence the outcome of AP but do provide patient comfort include the use of GI protectants, thermal support, and physical therapy. Antiemetics and promotility agents are useful for patients that are vomiting and for those with GI ileus. Intermittent nasogastric decompression is also recommended for patients with severe ileus; this will improve patient comfort, decrease nausea, and may decrease the risk of aspiration.

Treatment of concurrent diseases and of any inciting factors that may be identified is also important. Patients with overt DM, diabetic ketoacidosis (DKA), and those with persistent hyperglycemia should receive regular insulin, because strict glycemic control is important in the treatment of any critically ill patient. Cats with concurrent IBD may require glucocorticoid therapy.

124.7.5

Antibiotic Therapy

Routine use of prophylactic antibiotic therapy is controversial and is not recommended in most cases of AP because of the risk of inducing resistant bacterial strains. For patients with documented infections, broad-spectrum antibiotics with activity against gram-negative species can be started while awaiting results of culture and sensitivity testing. In human patients with SAP, there is an increased risk for pancreatic infection with greater than 30% necrosis, and infected pancreatic necrosis is a major risk factor for MODS and death; the incidence of infection appears to peak during the third week of hospitalization.[26-28] Despite numerous studies, however, it has not been shown convincingly that prophylactic antibiotic therapy improves outcome and, although conflicting, most of the recent consensus statements recommend against routine antibiotic prophylaxis.[26,27] In the veterinary literature antibiotic therapy is frequently recommended despite a lack of supporting evidence, and in fact it is thought that the incidence of infection is low. However, this is based on a small number of case reports and case series.* The actual incidence is unknown, because there have been no studies evaluating the incidence of infection in cats and dogs with AP.

Empiric antibiotic therapy may be reasonable for those patients that do not respond to other therapy and for those that initially respond but later deteriorate. However, every attempt to document infection in these patients should be made, including serial US or CT-guided FNA of areas of pancreatic and peripancreatic necrosis. Development of infection in extrapancreatic sites such as the urinary tract or respiratory tract may also occur.

* Reviewed in references 1, 2, and 33.

124.7.6 Surgery

Indications for surgery in patients with SAP are not always clear, and in the veterinary literature usually include those patients with infected pancreatic necrosis and those who continue to deteriorate despite aggressive medical treatment.[1,2,33] However, these patients are also very poor anesthetic risks, so the decision for surgical intervention should be made on an individual basis. In human medicine the trend over the last 20 years has been away from early aggressive surgical intervention to more conservative treatment strategies, and it is generally agreed that surgery is not indicated for most cases involving sterile pancreatic necrosis.[26-29] Debridement and/or drainage is indicated for patients with infected necrosis, although whenever possible delayed therapy is recommended to allow time for better demarcation of necrotic from viable tissue. This may also allow for use of less invasive interventions, including percutaneous and laparoscopic techniques. Successful percutaneous drainage of pancreatic pseudocysts has been described recently in veterinary patients.[25]

124.8 OUTCOME

Patients that survive an episode of pancreatitis may be normal, or may continue to have episodic flare-ups. Those that improve but again become ill several weeks to months after the initial presentation should be evaluated closely for development of local complications such as pancreatic pseudocyst or abscess, as well as for extrahepatic bile duct obstruction. Some patients may develop DM, chronic pancreatitis, and/or exocrine pancreatic insufficiency. A recent study suggests that subclinical, ongoing pancreatic inflammation may be relatively common in dogs that have had AP.[42]

124.9 CONCLUSION

Specific therapies using direct inhibitors of pancreatic secretion (atropine, somatostatin, glucagon, calcitonin) or using protease and other pancreatic enzyme inhibitors have generally proved unsuccessful. With the increasing recognition of the importance of inflammatory mediators in the progression to systemic organ dysfunction, much ongoing research is focused on the use of free radical scavengers and cytokine antagonists.

Continued advances in biochemical and diagnostic imaging modalities will help improve our ability to more rapidly and definitively diagnose AP in our patients, and may provide improved and objective means for determining and monitoring severity of disease. Decreases in morbidity and mortality in human patients with AP over the last 20 years have been attributed in part to development of scoring systems and other predictors of severity as previously discussed. In order to have meaningful evaluation of different therapies and to better understand the pathophysiologic mechanisms involved in canine and feline patients with AP, development of consensus definitions for clinical classification of AP and validation of severity scoring systems will be necessary.

124.10 SUGGESTED FURTHER READING*

EL Bradley: A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11-13, 1992. *Arch Surg*. **128**, 1993, 586, *Results of a symposium of 40 internationally recognized experts in human AP from various disciplines. Contains a* *series of definitions and a clinically based classification system for AP that were established by unanimous consensus. This objective system and terminology are now used widely in human medicine, allowing for earlier clinical diagnosis, assessment of severity, and more meaningful comparison of clinical trials and pathophysiologic studies among patient populations and various institutions.*

RS Hess, HM Saunders, TJ Van Winkle, et al.: Clinical, clinicopathologic, radiographic, and ultrasonographic abnormalities in dogs with fatal acute pancreatitis: 70 cases (1986-1995). *J Am Vet Med Assoc*. **213**, 1998, 665, *Retrospective study that evaluated clinical, laboratory, and diagnostic imaging findings in fatal cases of AP in dogs. In contrast to prior studies, used stringent inclusion criteria including histopathology to ensure that only dogs with AP were evaluated, although results may reflect only the most severe forms of AP.*

JL Holm, DL Chan, EA Rozanski: Acute pancreatitis in dogs. *J Vet Emerg Crit Care*. **13**, 2003, 201, *Well-written review article summarizing current information about diagnostic imaging, severity assessment, and treatment of AP in dogs and humans. A detailed review of the literature regarding AP in dogs is provided, with extensive references.*

JQ Jaeger, JS Mattoon, SW Bateman, et al.: Combined use of ultrasonography and contrast enhanced computed tomography to evaluate acute necrotizing pancreatitis in two dogs. *Vet Radiol Ultrasound*. **44**, 2003, 72, *Two imaging modalities were used to identify and evaluate pancreatic necrosis and vascular thromboses in two dogs with AP. The first report of US-guided FNA of pancreatic necrosis in dogs.*

AB Nathens, JRC Curtis, RJ Beale, et al.: Management of the critically ill patient with severe acute pancreatitis. *Crit Care Med*. **32**, 2004, 2524, *Results of a recent international consensus conference specifically focusing on critically ill patients with SAP. Guidelines differ from those previously published by concentrating on the challenges of caring for patients with SAP in the critical care environment. Provides a number of management recommendations derived from evidence-based medicine, in addition to an excellent up-to-date and critical review of the current literature.*

JM Steiner, DA Williams: Feline exocrine pancreatic disease, and Williams DA, Steiner JM: Canine exocrine pancreatic disease. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, St Louis, *Two chapters that provide a current and detailed review of pancreatitis in dogs and cats, particularly in the discussions of etiology, pathophysiology, and diagnostic evaluation.*

* See the CD-ROM for a complete list of references

125 Chapter 125 Acute Biliary Diseases of the Dog and Cat

Allyson C. Berent, DVM, DACVIM

125.1 KEY POINTS

- Biliary diseases in dogs and cats can present in a variety of ways: from benign incidental findings (biliary sludge, cholelithiasis, etc.) to severe life-threatening conditions (cholecystitis, gallbladder rupture, biliary mucoceles, and extrahepatic biliary duct obstructions).
- Animals with biliary tract dysfunction can have vague presenting complaints, such as vomiting, diarrhea, abdominal discomfort, icterus, ascites, and/or anorexia.
- Diagnostic modalities commonly include routine lab work and abdominal imaging (radiographs and ultrasound). A cholecystocentesis, laparoscopy, and/or surgical exploration may also be indicated.
- Classically, the prognosis for dogs with EHBDO is better than that for cats because of the cause of the obstruction: dogs most commonly experience obstruction from pancreatitis, whereas cats typically have neoplasia or cholangitis/triaditis.
- New minimally invasive interventions for non-ruptured biliary disease include endoscopic retrograde cholangiopancreatography (ERCP) and biliary stenting, both of which are currently under investigation for clinical patients.
- Early surgical intervention is imperative for animals with biliary tract rupture and should be considered in any patient with biliary tract disease that is declining clinically, regardless of the imaging findings.

125.2 INTRODUCTION

Biliary disease includes diseases of the gallbladder and biliary tract (both intrahepatic and extrahepatic). Clinically, diseases of the biliary system are considered either obstructive or nonobstructive. Obstructive diseases, with or without biliary tract rupture, are classically managed with surgery in animals, but laparoscopy, interventional radiology, or interventional endoscopy are usually considered primarily in humans.[1,2] Nonobstructive diseases are often managed medically, interventionally, or surgically. Biliary obstructive disease is most commonly due to pancreatitis in dogs and to neoplasia or inflammatory disease (pancreatitis, cholangitis, and inflammatory bowel disease, also know as *triaditis*) in cats.[3-5] In comparison with human medicine, biliary stone disease is relatively uncommon in small animal patients. The prognosis for dogs with extrahepatic biliary duct obstruction (EHBDO) is often better than that for cats, because pancreatitis is often self-limiting. Nonobstructive biliary disease occurs most commonly as a result of biliary sludge, cholecystitis, cholangitis (bacterial or immune mediated), and/or nonobstructive cholelithiasis. Less common causes include viral, fungal, parasitic, congenital diseases, or gallbladder infarction.[3-8] Biliary rupture can occur with either obstructive or nonobstructive diseases, as well as with trauma or secondary to diagnostic testing. Rupture of the biliary system causes bile peritonitis (bile is extremely irritating to extrabiliary or extraintestinal structures) and requires immediate surgical intervention. This chapter will discuss the physiology of the biliary system, clinical presentation of animals with biliary tract disease, diagnostic testing, specific disease entities, therapeutic approaches to these patients, and, finally, the prognosis and potential future interventions for animals with biliary tract disease.

125.3 PHYSIOLOGY

Bile is the product of the combination of water, conjugated bile acids, bile pigments, cholesterol, and inorganic salts.[3] It is transported from the bile ductules and ducts in the hepatic parenchyma to the cystic duct, common bile duct, and gallbladder. The common bile duct runs through the lesser omentum and enters the mesenteric wall of the duodenum. The canine common bile duct terminates in the duodenum near the minor pancreatic duct at the major duodenal papilla of the proximal duodenum. The feline common bile duct usually joins the major pancreatic duct before entering the duodenum at the papilla, similar to humans.[3] Once bile exits the extrahepatic biliary system into the duodenum, over 90% of bile salts are reabsorbed from the intestinal tract, transported back to the liver via the portal system, and recirculated. Bilirubin and biliverdin contribute to the yellow-green color of bile. Bile is deposited continuously into the biliary ducts and stored and modified in the gallbladder. Gallbladder emptying is controlled by both humoral (cholecystokinin, amino acids, fats, etc) and neural stimulation (vagal [parasympathetic] innervation). Along the tract from the bile ductules to the bile ducts and cystic duct, gallbladder, and common bile duct, different disease processes can occur, and often present in similar ways but require different interventions.

125.4 PRESENTATION OF BILIARY TRACT DISEASE

Icterus, vomiting, diarrhea, abdominal discomfort, lethargy, fever, and ascites are all common clinical findings in an animal with biliary tract disease. The patient's clinical signs may be slow and progressive (chronic pancreatitis, cholangitis, cholangiohepatitis, biliary mucocele, neoplasia, cholelithiasis) or acute and severe (biliary tract rupture, acute pancreatitis, necrotizing cholecystitis, emphysematous cholecystitis, EHBDO). An acute condition of the abdomen (see Chapter 123, Acute Abdominal Pain) may be caused by biliary leakage into the peritoneum, particularly if the fluid is septic.

125.5 DIAGNOSIS OF BILIARY TRACT DISEASE

History and physical examination findings are usually vague and rarely diagnostic for a specific cause of biliary tract disease. An icteric animal should be considered to have either prehepatic, hepatic, or posthepatic disease, although not all animals with biliary tract disease present with icterus. Further diagnostic testing can help to differentiate among the conditions that cause icterus. A complete blood count, serum biochemical profile, and urinalysis are indicated as part of a minimum database in dogs with such clinical signs. Icterus in the face of a normal or near-normal hematocrit (particularly those lacking a severe regenerative response) is usually suggestive of either hepatic or posthepatic icterus. Elevations in white blood cell parameters can be suggestive of an inflammatory condition (hepatitis, cholangiohepatitis, cholecystitis, bile peritonitis), whether the etiology is infectious, neoplastic, or immune mediated (see Chapter 126, Hepatitis and Cholangiohepatitis). The serum biochemical profile is usually more diagnostic. An increase in the alanine aminotransferase (ALT) is common if inflammation has ascended from the biliary tract to the liver, causing cholangiohepatitis (see Chapter 126, Hepatitis and Cholangiohepatitis). Increases in serum alkaline phosphatase (ALP), with or without hyperbilirubinemia, can be seen with obstructive or nonobstructive biliary diseases. Typically cats tend to have lower ALP elevations than dogs.[3] Gamma-glutamyltransferase (GGT) typically is elevated with cholestatic liver disease, although there are exceptions (feline hepatic lipidosis, biliary mucoceles). Hyperbilirubinemia is common, although bilirubinuria occurs before hyperbilirubinemia and should be assessed with routine urinalysis. Hypercholesterolemia may occur secondary to EHBDO, pancreatitis, or biliary tract rupture. If bile peritonitis is suspected, the abdominal fluid bilirubin level will be greater than the serum bilirubin.[3]

Biliary imaging is often necessary to differentiate hepatic from posthepatic icterus. Abdominal radiographs may reveal radiodense choleliths or air within the gallbladder (emphysematous cholecystitis). Animals with pancreatitis could have a loss of serosal detail in their right cranial abdomen (see Chapter 124, Acute Pancreatitis). Contrast radiographs of the biliary system (percutaneous cholecystography) have been described, but alternative safer imaging modalities often yield comparable information (abdominal ultrasound, computed tomography, and endoscopic retrograde cholangiopancreatography [ERCP]).[1,2,9]

Ultrasonography is the most useful and available noninvasive technique to differentiate intrahepatic from extrahepatic disease. It can identify lesions within the gallbladder and biliary tract (biliary mucocele, choleliths, biliary debris or "sludge," gas associated with emphysematous cholecystitis, tumors), most biliary tract obstructions (secondary to tumors, choleliths, pancreatitis, debris), and peritoneal effusion due to biliary tract rupture (secondary to a biliary mucocele, trauma, cholecystocentesis, obstruction). Echogenic contents within the gallbladder, or biliary sludge, are often considered an incidental finding by most radiologists, although they can also occur secondary to stagnant biliary flow and may be suggestive of biliary or nonbiliary disease.[10,11] During states of biliary stasis, water is absorbed from the bile and it becomes thicker, resulting in sludge which can be obstructive as it passes.

Biliary sludge should be differentiated from a biliary mucocele, which can be a life-threatening condition and should be considered a significant finding and followed carefully.[4,6,7] Mucoceles cause distention of the gallbladder resulting from an inappropriate accumulation of mucus and inspissated bile. Ultrasound examination reveals an immobile bile pattern with a finely striated and stellate appearance, often referred to as a *kiwi gallbladder*. [11] A significant number of cases (15%) with biliary mucoceles who do not have ultrasonographic evidence of biliary rupture are found to be ruptured during surgical exploration, making clinical impression of patient progression the most important parameter for therapeutic decision making.[6,7,11] Animals that have been fasted or are anorexic may also have a distended gallbladder, which can be misdiagnosed as a biliary obstruction. The progression of ultrasound changes with biliary tract obstructions have been documented.[3,8] Dilation of the gallbladder and a loss of the gallbladder neck tapering typically occurs within 24 hours of duct ligation; after 48 hours dilation of the common bile duct is seen; after 72 hours dilation of the extrahepatic biliary ducts are present; and after approximately 7 days diffuse dilation of the intrahepatic biliary tree are observed.[3,8] Gallstones are often hyperechoic foci and display acoustic shadowing from within the gallbladder or biliary tree. Cholecystitis may cause gallbladder wall thickening or edema, and a double-wall appearance has been described.[3,8]

Cholecystocentesis can be performed diagnostically to obtain bile for cytology and aerobic and anaerobic culture, as well as therapeutically for decompression in the case of obstructive disease, although therapeutic intervention needs further investigation before it is recommended for clinical use.[3,12] To prevent bile leakage into the abdomen, reports have recommended performing this procedure through the liver parenchyma.[13]

A diagnostic peritoneal lavage (see Chapter 156, Diagnostic Peritoneal Lavage), laparoscopy, and/or surgical exploration should be performed when a ruptured biliary tract is suspected, or there is evidence of EHBDO, neoplasia, cholelithiasis, biliary mucoceles, trauma, necrotizing cholecystitis, or emphysematous cholecystitis.[3,4,6,7] Patency of the biliary tract can be evaluated carefully during surgical exploration. Nuclear scintigraphy is rarely used to define canine or feline biliary tract diseases, although this technique has been performed in humans.[3,14]

125.6 DISEASES OF THE BILIARY SYSTEM

125.6.1 Obstructive Disease

Pancreatitis may cause biliary obstruction with severe ductal inflammation, scar tissue formation, or abscess formation (see Chapter 124, Acute Pancreatitis). This is the most common cause of biliary tract obstruction in dogs and the second most common in cats secondary to neoplasia. Chronic pancreatitis can cause fibrosis or scar tissue formation at the common bile duct and result in biliary obstruction, although signs are often more insidious in nature. Treatment of EHBDO due to pancreatitis is often medical, although percutaneous biliary tract drainage has been described in a small case series[12] and ERCP with temporary bile duct stenting commonly is performed in humans, and is currently under investigation in animals.[2,15] If medical management fails, a cholecystoduodenostomy or cholecystojejunostomy may be considered.[3,4]

The most common neoplastic causes of biliary obstruction include biliary or pancreatic adenocarcinoma, or duodenal neoplasia causing obstruction of the major or minor duodenal papilla. Lymphoma can also cause EHBDO. Surgery for pancreatic neoplasia is often unrewarding, because most tumors are malignant and have already metastasized at the time of diagnosis. Cholecystojejunostomy may be palliative. The prognosis is typically very poor for neoplasia-induced obstructions.[3,4] Endoscopic stent placement, using either polyurethane or self-expanding metallic stents, for common bile duct obstruction using ERCP is performed routinely in humans and is currently under investigation in small animals.[1,2,16]

Cholecystoliths, typically composed of calcium, cholesterol, and/or bile salts, are usually incidental findings on abdominal radiographs. However, a surgical cholecystectomy or choledochotomy is required if they result in EHBDO. Biliary stones are uncommon in veterinary patients and rarely result in obstruction.

Biliary mucoceles have been described as a cause of biliary obstruction in dogs. A mucocele is an abnormal accumulation of mucus and inspissated bile that distends the gallbladder and often causes some degree of EHBDO.[6,7,11] The pathogenesis of the disease is unknown and does not appear to have an inflammatory component. Histologically, hyperplasia of mucus-secreting glands within the gallbladder mucosa and an abnormal accumulation of mucus within the lumen are reported. Because of the apparent disease of the gallbladder wall, surgical removal is recommended to avoid rupture secondary to pressure necrosis or ischemia.[3,4,6,7] Sensitivity of rupture detection with ultrasound is approximately 85.7%.[6] Fifty to sixty percent of dogs with mucoceles were documented to have gallbladder rupture at the time of surgery. Cocker Spaniels and Collie breeds may be overrepresented, and infections are sometimes associated with mucoceles. Twenty-three percent of dogs with mucoceles in one study had concurrent pituitary-dependent hyperadrenocorticism, increasing the risk of associated infection.[6]

125.6.2 Nonobstructive Biliary Tract Disease

Nonobstructive biliary tract disorders include complications resulting from bacterial infection of the biliary system, biliary mucoceles, cholecystitis (necrotizing, emphysematous, bacterial, parasitic), pancreatitis, cholelithiasis, and/or neoplasia.

Cholecystitis, or inflammation of the gallbladder, can be either sterile or nonsterile in nature. It usually involves both the intrahepatic and extrahepatic biliary ducts.[3,8] The patient's condition can often be stabilized medically with antibiotics, choleretics, and time. However, if episodes recur, or if signs fail to resolve with conservative management, a cholecystectomy may be required.[3]

Bacteria most likely enter the biliary system by ascending from the gastrointestinal (GI) tract in a retrograde fashion. Bacterial infections in the biliary tract are occasionally treated with appropriate medical therapy, including antibiotics (ideally based on aerobic and anaerobic culture and sensitivity results). Bacterial colonization of the biliary system has been reported in animals with cholangitis, cholangiohepatitis, cholecystitis, choledochitis, pancreatitis, and focal suppurative or multiple hepatic abscess formation.[3,8] The inflammation is limited to the gallbladder in animals with cholecystitis. If the inflammation or infection progresses, cholangitis or cholangiohepatitis may result. Cholangiohepatitis is seen more commonly in cats than dogs (see Chapter 126, Hepatitis and Cholangiohepatitis). When the gallbladder is infected with gas-producing bacteria (e.g., *Escherichia coli* or *Clostridium perfringens*), emphysematous cholecystitis ensues. Gas production may result in a radiolucency on radiographs in the area of the gallbladder, or acoustic shadowing in the gallbladder with abdominal ultrasound.

Necrotizing cholecystitis may cause severe weakening of the biliary wall and subsequent rupture of the biliary tract. The pathogenesis of cholecystitis is poorly understood, and the relationship between cholangitis and cholangiohepatitis in dogs and cats is questionable. Recurrent bacterial infections or evidence of biliary rupture are indications for surgical exploration and cholecystectomy. Bacteria can be isolated from percutaneous aspiration or surgically obtained bile and liver cultures. Various bacterial isolates have been identified; however, *E. coli, Clostridium* spp, and *Streptococcus* spp have been reported most commonly.[3,8] Biliary parasites are uncommon. *Platynosomum fastosum* may infect cats from warm, tropical climates; *Amphimerus pseudofelineus* has been associated with cholangitis, cholangiohepatitis, and common bile duct distention in cats; and *Metorchis conjunctus* and *Eurytrema procyonis* may be found in the feline biliary tract.[3] Ultrasonography or fecal sedimentation can aid in diagnosis, and praziquantel is the treatment of choice for most fluke infestations.

Gallbladder infarction has been found on histopathologic examination in 12 dogs and may result in gallbladder rupture.[17] Some of these dogs also had evidence of infarction in other organs, causing speculation that a systemic hypercoagulable state might have led to infarction of biliary structures. This condition was not associated with cholecystitis.

Neoplasia of the biliary system does not necessarily result in obstructive disease. Bile duct carcinomas have been reported, and metastasis is common at the time of clinical diagnosis.[3] Congenital conditions like Caroli's syndrome (congenital malformation of bile ducts) or polycystic disease can cause congenital dilation of both intrahepatic and extrahepatic biliary ducts throughout the liver. These animals are usually young and the diagnosis is based on histopathologic evaluation.[18]

125.6.3 Biliary Tract Rupture

Extrahepatic biliary duct or gallbladder rupture results in sterile or septic bile peritonitis, and is extremely irritating to the visceral and parietal peritoneal surface. The most common causes of bile peritonitis are necrotizing cholecystitis, trauma, and cholelithiasis.[3-5] Biliary tract rupture can occur with either obstructive or nonobstructive diseases (Box 125-1). Septic bile peritonitis is associated with a higher postsurgical mortality (55%) than sterile suppurative bile peritonitis (13%).[3,4] Bile peritonitis due to a biliary mucocele can be diagnosed by the identification of mucinous material in the abdominal cavity, on ultrasonographic evaluation, or during surgery.[6,7]

125.7 TREATMENT OF BILIARY TRACT DISEASE

125.7.1 Surgical Management

Animals with evidence of bile peritonitis should be considered surgical emergencies, making early diagnosis of biliary tract rupture imperative. Animals with infected bile in the peritoneal cavity hold a worse prognosis, and perioperative antibiotic therapy pending culture and sensitivity results is imperative.[3,6,7] A clear indication for surgery in animals with biliary tract disease is often difficult if a ruptured tract is not identified. Most patients with biliary obstruction require surgical decompression to prevent rupture, although animals with pancreatitis often respond to medical management, time, and decompressive percutaneous cholecystocentesis (if necessary). Because surgical intervention in dogs with pancreatitis-induced EHBDO has a reported mortality rate of 50%, conservative management of these cases is preferable in most patients.[4] With the introduction of endoscopic biliary stent placement in small animal patients, a better alternative for animals with nonruptured, obstructive disease may be available soon.

Indications for surgical exploration include worsening clinical status despite appropriate medical treatment, an increasing total bilirubin, ALP, or GGT levels on repeat serum biochemical profiles, increasing white blood cell counts with a degenerative left shift, and/or increasing size of the biliary system on serial ultrasound examinations. With biliary obstruction or traumatic rupture, rerouting procedures of the biliary tract are often warranted, although biliary stent placement may decrease anesthesia time in these debilitated patients and avoid the risk of dehiscence with rerouting techniques.[19] When the patency of the bile duct is confirmed, or can be established, and significant gallbladder disease exists, a cholecystectomy is indicated. The type of procedure performed has not been associated with differences in outcome following surgery, although stent placement may shorten the anesthesia time.[19] At the time of surgery, a thorough abdominal exploration with careful assessment of the liver, pancreas, and GI tract should be performed, and specimens for histopathology and bacterial culture (aerobic and anaerobic) should be obtained, if indicated. Culture of bile often yields positive bacterial growth. Because these patients may have a poor nutritional status before surgery and often remain anorexic for a significant period postoperatively, jejunostomy or gastrojejunostomy tube placement during surgery may prove beneficial. Postoperatively, dehiscence of the biliary surgical site may result in bile peritonitis and patients should be monitored for this complication carefully.

125.7.1.1 Box 125-1 Causes of Biliary Tract Disease

125.7.1.1.1 Obstructive

Pancreatitis

Neoplasia (lymphosarcoma, biliary adenocarcinoma, pancreatic adenocarcinoma)

Cholelithiasis

Cholangitis

Inspissated bile, biliary sludge

Biliary mucocele (not commonly obstructive)

Duodenal disease (foreign body, fibrosis, stricture, neoplasia)

125.7.1.1.2 Nonobstructive

Pancreatitis

Neoplasia

Cholelithiasis

Cholecystitis (emphysematous, necrotizing, lymphoplasmacytic)

Biliary mucocele

Gallbladder infarction

Congenital disease (Caroli's syndrome, polycystic kidney disease)

Biliary rupture

Blunt trauma

Iatrogenic (surgical dehiscence, percutaneous cholecystocentesis)

Biliary mucocele

Cholelithiasis

Neoplasia

Cholecystitis

Pancreatitis

Inspissated bile, biliary sludge

Biliary mucoceles are now reported more commonly in dogs. Cholecystectomy is the preferred treatment for most affected dogs, although there is little evidence in the literature regarding medical treatment of such conditions.[4,6,7,11] Up to 60% of biliary mucoceles are found ruptured at the time of surgery, regardless of clinical suspicion preoperatively. Because of the high incidence of rupture and the histologic findings of mucosal hyperplasia, pressure necrosis, and ischemia, surgical exploration is often indicated in these patients.

125.7.2 Medical Management

Pancreatitis, bacterial cholecystitis, benign biliary sludge, and small, nonobstructive choleliths are the most common disorders of the biliary tract for which medical treatment alone is indicated initially. Any one of these conditions may require surgery if the medical response is not adequate, therefore frequent monitoring for patient changes is imperative. Dehydration and/or hypovolemia often occur and should be carefully assessed and treated with crystalloids and/or colloids, as indicated (see Chapters 64 and 65, Daily Intravenous Fluid Therapy and Shock Fluids and Fluid Challenge, respectively). Postoperative hypotension is a negative prognostic indicator for animals with surgically treated biliary disease and may occur secondary to hypovolemia, endotoxemia, or systemic inflammatory response syndrome.[4]

Frequent monitoring of clinical signs, arterial blood pressure, and central venous pressure will help identify hypotensive patients. Pressor support should be considered if hypotension persists following adequate volume replacement (see Chapter 176, Vasoactive Catecholamines). Hypoproteinemia frequently occurs in patients with bile peritonitis, pancreatitis, and SIRS, indicating the need for colloidal support. Nutritional status should be assessed carefully and support provided. Enteral nutrition in normotensive patients is the preferred route, although jejunostomy feedings are useful in animals that are vomiting. If jejunostomy tube feedings are not possible, total or partial parenteral nutrition should be considered. Jejunostomy tubes typically 545 546 are placed surgically, although new minimally invasive fluoroscopic guided methods are now possible (gastrojejunostomy, esophageal jejunostomy, and nasojejunostomy tubes).

Antibiotic support should be based on bacterial culture and susceptibility patterns from samples collected surgically or percutaneously (with ultrasound guidance). Empiric antibiotic therapy pending culture results often includes intravenous fluoroquinolones and ampicillin, or fluoroquinolones and metronidazole, all of which have enterohepatic uptake. Pain should be addressed proactively, because most biliary diseases are associated with significant patient discomfort (see Chapter 161, Pain and Sedation Assessment). However, care should be taken to avoid ileus secondary to analgesic use in animals with biliary tract disease.

Coagulation abnormalities are common in animals with biliary obstruction and hepatic dysfunction, especially those that lack vitamin K absorption secondary to bile duct obstruction. Parenteral vitamin K_1 therapy may benefit animals with cholestatic disease. If bleeding is a concern, fresh frozen plasma transfusions should be considered (see Chapter 66, Transfusion Medicine). Treatment guidelines for patients suffering from pancreatitis can be found in Chapter 124, Acute Pancreatitis.

125.7.3 Long-Term Management

Resolution of jaundice is a gradual process. It may take weeks to months for cholestatic and hepatocellular enzyme levels to normalize completely. Medical treatment often consists of antibiotic therapy, diet change to minimize the risk of pancreatitis, inflammatory bowel disease or food hypersensitivity, and/or drugs that alter biliary secretion, depending on the nature of the primary disease process. Ursodeoxycholic acid (Actigall) is a hydrophilic bile acid that increases the water content of biliary secretions, encourages choleresis, decreases inflammation and immune-mediated reactions, and lessens the hepatotoxic nature of bile acids. It is imperative that this therapy not be given to animals with an obstructed biliary tract, because increasing the quantity of biliary secretions and gallbladder motility may lead to biliary rupture.[20]

125.8 PROGNOSIS

Mortality has been shown to increase after surgery in dogs with septic bile peritonitis, prolonged partial thromboplastin times, or lower postoperative mean arterial pressures in one study.[4] The perioperative mortality rate for dogs that undergo surgery is reported to be 28% to 64%.[4,6,7,11,21] Various studies have reported mortality rates following biliary surgery in animals with pancreatitis (50%), necrotizing cholecystitis (25%), biliary mucoceles (21.7% to 32%), and trauma (0%).[4,6,7] It is imperative that a diagnosis of biliary obstruction and surgical intervention, if needed, occur early. Overall, biliary tract diseases in small animal patients are associated with a fair prognosis, although outcome is dependent on the underlying disease process and timely intervention.

125.9 FUTURE GOALS AND THERAPIES

Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic biliary stent placement is an effective initial treatment for icteric human patients with bile duct obstruction (due to bile duct strictures, neoplasia, choleliths, pancreatitis, and obstructive cholangitis). It is now considered the standard of care for many biliary conditions.[1,2,15] This procedure is minimally invasive, associated with minimal discomfort, and can be performed with heavy sedation in humans, avoiding long anesthesia procedures in unstable patients. The procedure has been performed in research Beagles and a small group of clinical canine cases,[15] showing potential promise in small animals. Clinical work is being performed in this area for both ERCP and biliary stenting at the author's institution. Laparoscopic cholecystectomy is also becoming more popular in small animal patients. Percutaneous drainage of the biliary system using fluoroscopy and interventional radiology techniques also shows great potential, but further investigation is required.

125.10 SUGGESTED FURTHER READING*

LL Sartor, LA Trepanier: Rational pharmacologic therapy of hepatobiliary disease in dogs and cats. *Comp Cont Educ Pract Vet*. **25**, 2003, 432, *A nice review of various types of polypharmacy typically employed for hepatobiliary disease in small animals*.

MD Willard, TW Fossus: Diseases of the gallbladder and extrahepatic biliary system. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Elsevier, St. Louis, *A nice chapter that organizes the various types of biliary tract diseases*.

DR Worley, HA Hottinger, HJ Lawrence: Surgical management of gallbladder mucoceles in dogs: 22 cases (1999-2003). *J Am Vet Med Assoc*. **225**, 2004, 1418, *A good discussion of the preoperative, intraoperative, and postoperative findings in dogs with biliary mucoceles that were treated surgically*.

* See the CD-ROM for a complete list of references

126 Chapter 126 Hepatitis and Cholangiohepatitis

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126.1 KEY POINTS

- Although many causes of hepatitis and cholangiohepatitis have been described in dogs and cats, the etiology in many cases remains unknown.
- A suspicion of hepatitis or cholangiohepatitis may be based on supportive historical, physical examination, and clinicopathologic findings that are similar for most causes of hepatic disease. A diagnosis of hepatitis or cholangiohepatitis is ultimately made via histopathologic evaluation of hepatic tissue.
- The mechanisms of hepatocellular injury in animals with hepatitis and cholangiohepatitis are poorly understood. Elucidation of these mechanisms may provide the basis for future therapeutic options.
- Successful treatment of the patient with hepatitis or cholangiohepatitis involves addressing the underlying disease or inciting cause and providing aggressive symptomatic therapy and supportive care.

126.2 INTRODUCTION

Hepatitis is defined as any inflammatory cell infiltrate within the hepatic parenchyma, and the term *cholangiohepatitis* describes extension of that inflammation to include the intrahepatic bile ducts.[1] A diagnosis of these conditions is based on histopathologic examination of hepatic biopsy specimens. The histopathologic appearance will give clues as to the duration of the inflammation. Acute hepatitis is characterized by a combination of inflammation, hepatocellular apoptosis, necrosis, and possibly regeneration, but there is a lack of fibrosis. Chronic hepatitis (CH), on the other hand, is identified by the presence of fibrosis, proliferation of ductular structures, and regenerative nodules in addition to the inflammatory infiltrate.[2] The type of inflammatory cellular infiltrate may give the clinician some clues regarding the etiology. Occasionally, etiologic agents will be identified within biopsy specimens. However, the etiology remains unknown for many cases of hepatitis and cholangiohepatitis in dogs and cats. This chapter will discuss the clinical presentation of animals with hepatitis and cholangiohepatitis and outline the most commonly recognized clinical syndromes with respect to diagnosis and treatment of the specific disease. Effective treatment of patients with hepatitis or cholangiohepatitis includes specific therapy of any identified inciting cause and aggressive symptomatic and supportive therapy. A discussion of symptomatic treatment and supportive therapy for the sequelae of hepatitis and cholangiohepatitis can be found in Chapter 127, Hepatic Failure.

126.3 HISTORICAL FINDINGS

In general, the historical findings associated with hepatitis are nonspecific, as with most types of liver disease. Exposure to certain etiologic agents or toxins may be ascertained from the owner and history and thus raise the suspicion for hepatic involvement. It is important to remember that because of the large reserve capacity of the liver, a short duration of clinical signs does not necessarily indicate acute disease. Animals with CH may not show outward clinical signs until a significant portion of their hepatic function is affected. Presenting owner complaints for animals with hepatitis may include vomiting, diarrhea, anorexia, lethargy, polyuria, polydipsia, abdominal distention, dysuria, neurologic abnormalities associated with hepatic encephalopathy or vascular accidents, and icterus.

126.4 PHYSICAL EXAMINATION FINDINGS

Similar to historical findings, the physical examination findings in animals with hepatitis are often nonspecific. Icterus, when present in the absence of hemolytic anemia, suggests disease of the hepatic parenchyma or extrahepatic biliary system. Animals with acute hepatitis are more likely to have fever and abdominal pain, and those with CH are more likely to have ascites. Hepatomegaly may be present in some patients, especially those with acute hepatitis. Many animals with hepatitis will not have any of these physical abnormalities present on the initial examination, and serum biochemical changes in those cases are likely to direct the clinician toward the liver as the site of disease.

126.5 MECHANISMS OF HEPATOCELLULAR INJURY

The pathogenesis whereby hepatitis and cholangiohepatitis lead to hepatocellular necrosis and apoptosis is incompletely understood. Experimental studies have suggested many mechanisms of hepatocellular injury, but their specific evaluation in dogs and cats with hepatitis is lacking. Mechanisms of hepatocellular injury that are not specific to hepatitis include tissue hypoxia, lipid peroxidation, intracellular cofactor depletion, intracellular toxin production, cholestatic injury, endotoxic insults, and hepatocyte plasma membrane injury.[3]

Hepatocytes are especially susceptible to anoxia because the liver receives a mixture of venous and arterial blood. Hypoxic damage quickly leads to plasma membrane and cytosolic organelle injury secondary to adenosine triphosphate (ATP) depletion. Free radicals may cause oxidative cellular injury that can result in lipid peroxidation and subsequent plasma membrane damage.

Cellular toxins may bind to nucleic acids and inhibit protein synthesis. Cholestasis causes retention of bile acids that directly damage cellular organelles. Endotoxins work via various mechanisms, most of which involve stimulation of inflammatory cells to produce inflammatory mediators (cytokines such as prostaglandins and leukotrienes) that perpetuate hepatitis. Experimental work in mouse models suggests an important role for tumor necrosis factor-alpha (TNF-α) in the initiation and perpetuation of hepatitis. TNF-α, production of which is induced by the interaction of the costimulatory molecules CD154 on T cells and CD40 on hepatocytes and Kupffer cells, stimulates hepatocyte apoptosis through the Fas-Fas ligand pathway.[4] A better understanding of the complex mechanisms of hepatocellular injury in animals with hepatitis may encourage the development of novel therapeutic modalities for affected patients.

126.6 CAUSES OF HEPATITIS AND CHOLANGIOHEPATITIS IN DOGS AND CATS

Box 126-1 lists the reported causes of hepatitis and cholangiohepatitis in dogs and cats. A complete discussion of all disease entities is beyond the scope of this chapter. A discussion of the most common clinical syndromes follows.

126.6.1

Idiopathic Causes

126.6.1.1

Feline Cholangitis-Cholangiohepatitis Complex

The feline cholangitis-cholangiohepatitis complex is one of the most common hepatobiliary disorders in cats.[5] This syndrome has been reported in dogs[6] but is primarily a feline disease. Several classification schemes have been proposed to define the various elements of this syndrome. Recently, the world small animal veterinary association (WSAVA) Liver Standardization Group proposed a classification system that divides feline inflammatory liver disease into two main categories: neutrophilic cholangitis and lymphocytic cholangitis.[7]

126.6.1.1.1

Box 126-1 Causes of Hepatitis and Cholangiohepatitis in Dogs and Cats

126.6.1.1.1.1

Idiopathic

Canine chronic hepatitis

Feline cholangitis-cholangiohepatitis complex

Nonspecific reactive hepatitis

Lobular dissecting hepatitis

126.6.1.1.1.2

Viral

Infectious canine hepatitis (adenovirus type I)

Acidophil cell hepatitis

Herpesvirus (neonates)

Feline infectious peritonitis

126.6.1.1.1.3

Bacterial

Feline cholangitis-cholangiohepatitis complex

Leptospirosis

Bartonellosis

Tyzzers disease *(Clostridium piliformis)*

Salmonellosis

Listeriosis

Tularemia

Brucellosis

Yersiniosis

Helicobacter spp

Mycobacteria

Septicemia

126.6.1.1.1.4 Rickettsial

Ehrlichiosis

Rocky Mountain spotted fever

126.6.1.1.1.5 Protozoal

Toxoplasmosis

Neosporosis

Leishmaniasis

Cytauxzoonosis

Hepatozoonosis

- Schistosomiasis
- Coccidiosis

126.6.1.1.1.6

Parasitic

- Visceral larval migrans
- Dirofilariasis (caudal vena caval syndrome)
- Liver fluke migration

126.6.1.1.1.7

Fungal

- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Aspergillosis (disseminated)
- Phycomycosis
- Algal
- Protothecosis

126.6.1.1.1.8

Select Drugs and Toxins

- Amiodarone
- Aspirin
- Carprofen
- Halothane

Ketoconazole

Lomustine

Methimazole

Phenobarbital

Phenytoin

Primidone

Trimethoprim/sulfadiazene or sulfamethoxazole

126.6.1.1.2 Neutrophilic Cholangitis

Neutrophilic cholangitis (NC) is characterized by infiltration of neutrophils within the wall or lumen of intrahepatic bile ducts. This disease can be seen in both acute and chronic stages. In the acute stage, edema and neutrophilic inflammation may extend into the portal areas. In the chronic stage, a mixed inflammatory infiltrate may be noted in portal areas, along with varying degrees of fibrosis and bile duct hyperplasia. This syndrome was previously referred to as *acute cholangiohepatitis* or *suppurative cholangitis-cholangiohepatitis*. [8,9] Extrapolating from data using other classification schemes, it is likely that affected cats will be young to middle-aged with a male predisposition. Duration of illness is usually short (<5 days). Anorexia, weight loss, lethargy, and vomiting are common. Many cats are febrile and most animals have elevated serum alanine aminotransferase (ALT) activity at the time of presentation, with fewer numbers having elevated alkaline phosphatase (ALP) activity. Icterus is present in over 50% of cases. Cholangiohepatitis in cats has been associated with inflammatory bowel disease (IBD) and pancreatitis, 548 549 [10] and many investigators believe that NC is the result of an ascending bacterial infection from the gastrointestinal (GI) tract. However, bacterial organisms have been isolated inconsistently from cases reported in the literature. When isolated, common bacterial species include *Escherichia coli, Enterococcus* spp, *Clostridium* spp, *Bacteroides* spp, *Actinomyces* spp, and *Streptococcus* spp. Hepatic tissue, bile, or both should be submitted for aerobic and anaerobic culture as part of the diagnostic workup for any cat suspected of having hepatitis. Treatment with a broad-spectrum antibiotic combination aimed at enteric flora is recommended pending results of culture and sensitivity testing. Prognosis for cats with NC is typically good with aggressive treatment, although sequelae may include bile duct obstruction, acute necrotizing pancreatitis, sepsis, and multiple organ dysfunction.

126.6.1.1.3 Lymphocytic Cholangitis

Lymphocytic cholangitis (LC) is a chronic form of disease that is characterized by a mixed inflammatory infiltrate (typically small lymphocytes, or lymphocytes and plasma cells) within portal areas with associated signs of chronicity including bile duct proliferation, bridging fibrosis, and pseudolobule formation.

Inflammation within the walls or lumens of intrahepatic bile ducts may be present, but is not a specific hallmark of the disease. LC probably includes a wide spectrum of clinical diseases with varying severity and clinical significance. LC likely includes syndromes that have previously been referred to as *chronic cholangiohepatitis, nonsuppurative cholangitis-cholangiohepatitis* and *lymphocytic portal hepatitis*. [8-11] Extrapolating from data using other classification schemes, it seems that cats with LC tend to be older than those with NC. Clinical signs are similar to those seen in NC with the exceptions that fever is uncommon, the onset of illness is more insidious, and the duration of illness tends to be longer in cats with LC. Elevations of serum ALT, ALP, and total bilirubin are common as in NC, but cats with LC tend to have higher ALP than those with NC. The etiology of LC is unknown, although a chronic response to an ascending bacterial infection from GI flora and an association with IBD and pancreatitis (as seen with NC) has been suggested.[8,9] Active infection has been rarely documented in cats with LC. Treatment typically involves immunosuppressive glucocorticoid therapy in animals with no evidence of infection. Treatment with ursodeoxycholic acid (10 to 15 mg/kg PO q24h) has anecdotal and theoretic benefits, although no clinical studies examining its efficacy in cats have been published. Prognosis is typically good with appropriate management.

126.6.1.2 Canine Chronic Hepatitis

Although many causes of chronic hepatic inflammation in dogs have been identified, the term *chronic hepatitis* (CH) describes a progressive necroinflammatory disease of unknown etiology that is common in the canine population.[1] Evidence supports an immune-mediated process as the perpetuating factor,[1,12,13] although it is unclear whether the disease is autoimmune in nature or if an outside insult incites the immune response. Because of the chronic nature of the disease and the large reserve capacity of the liver, many affected animals are not identified until the onset of fulminant hepatic failure. However, increasing numbers of cases are now being identified at an earlier asymptomatic stage as a result of elevated hepatic enzyme activity that is noted on routine serum biochemical screening.

Animals of any age and sex are affected, although middle-aged female dogs may be overrepresented. CH is seen with increased frequency in certain breeds (Box 126-2), suggesting a familial predisposition. No specific diagnostic findings separate CH from other causes of hepatitis. Ultimately, the diagnosis is based on histopathologic examination of liver tissue revealing inflammation (usually lymphocytic and plasmacytic), piecemeal or bridging necrosis, and possibly fibrosis and/or hyperplasia of ductular structures and the absence of an identifiable underlying cause.[1] The optimal treatment protocol for animals with CH has not been well studied, but immunosuppressive therapy is the mainstay of treatment. Corticosteroids are the only class of drug shown to potentially provide benefit[14] and their use is indicated in patients with signs of hepatic failure. Other immunomodulatory drugs that may be used include ursodeoxycholic acid, metronidazole, azathioprine, and cyclosporine. Copper chelation may be beneficial when copper retention is a significant contributing factor. The overall prognosis is difficult to ascertain because asymptomatic animals may have a slowly progressive course and excellent prognosis. However, once hepatic failure and/or cirrhosis develops, the prognosis is poor.

126.6.1.2.1 Role of Copper

The role of copper in the pathogenesis of CH is unclear. Elevated hepatic copper levels have been identified in many dogs with CH, but because biliary excretion is the major mechanism of maintaining copper homeostasis, any cause of cholestasis would be expected to increase hepatic copper levels.[12] However, it has been shown in the Bedlington Terrier that elevated copper levels (caused by an inherited defect in excretion) will lead to CH and cirrhosis.[1] However, it may be difficult to determine which came first, the copper accumulation or the hepatitis. A propensity for increased hepatic copper levels in association with CH has been described for many breeds in addition to the Bedlington Terrier, and these are listed in Box 126-2.

A suspected primary hepatic copper storage disorder has also been reported in one cat.[15] Whether the copper accumulation is a primary or secondary event, it is possible that the excessive copper is damaging to hepatocytes. Copper chelation treatment has improved or resolved the hepatic pathologic findings in a group of Doberman Pinschers with elevated hepatic copper levels and subclinical CH.[16] It is recommended that hepatic tissue be harbored for copper quantification in any dog undergoing liver biopsy. If elevated levels are identified, a reduction of dietary copper and chelation with D-penicillamine (10 to 15 mg/kg q12h, given 1 to 2 hours before feeding) or trientine (10 to 15 mg/kg q12h, given 1 to 2 hours before feeding) are likely to be beneficial.

126.6.1.2.1.1

Box 126-2 Breeds Predisposed to Chronic Hepatitis

*Proven or suspected copper-associated hepatopathy.

- American Cocker Spaniel
- Bedlington Terrier*
- Dalmatian*
- Doberman Pinscher*
- English Cocker Spaniel
- Labrador Retriever*
- Skye Terrier*
- Standard Poodle
- West Highland White Terrier*

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126.6.1.3

Nonspecific Reactive Hepatitis

Nonspecific reactive hepatitis is a histologic diagnosis that describes the liver's response to a variety of extrahepatic disease processes. The lesion is characterized by widespread inflammatory infiltrates (usually lymphocytes and plasma cells) in the portal areas and parenchyma in the absence of hepatocellular necrosis.[2] Identification of this lesion should alert the clinician that a liver-specific problem is unlikely and that further investigation into the underlying disease process is necessary.

126.6.2 Viral Causes

Viral hepatitis is uncommon in dogs and cats. Most viral infections carry a poor prognosis. Specific therapy is not available or has not been evaluated. Symptomatic therapy and supportive care are therefore the primary therapeutic options.

126.6.2.1 Infectious Canine Hepatitis

Infectious canine hepatitis is caused by canine adenovirus type I. This disease has become quite rare owing to extensive vaccination protocols using the cross-reacting adenovirus type II. As such, the disease is only seen in young, unvaccinated dogs. The degree of antibody response determines the severity of disease, with a poor response resulting in an acutely fatal syndrome. Animals that mount an appropriate response may recover or develop CH. Corneal edema and anterior uveitis may develop in animals that recover from acute illness. The diagnosis is made by histopathologic identification of large basophilic to amphophilic intranuclear inclusion bodies within hepatocytes and Kupffer cells that are identified during the first week of infection.[12] Histopathology will also reveal multifocal coagulation necrosis and a neutrophilic inflammatory infiltrate that may not be present in animals with severe acute infection.

126.6.2.2 Feline Infectious Peritonitis

Feline infectious peritonitis (FIP) is caused by the feline enteric coronavirus. FIP can affect any organ in the body. Cats with hepatic involvement often have elevated activities of ALT and aspartate aminotransferase (AST) and develop hyperbilirubinemia as the disease progresses. Histologic lesions include multifocal necrosis (often around blood vessels) with associated infiltration with neutrophils and macrophages. Pyogranulomatous lesions may be noted on the liver capsule.[12] When hepatic involvement occurs, the disease is uniformly fatal. Because there is no definitive treatment, supportive care is the mainstay of treatment.

126.6.3 Bacterial Causes

126.6.3.1 Leptospirosis

Leptospirosis is caused by any one of several serovars of spiral bacteria belonging to the species *Leptospira interrogans* sensu lato. The commonly isolated serovars in small animals include *L. icterohaemorrhagiae, L. canicola, L. pomona, L. hardjo, L. grippotyphosa,*and *L. bratislava*. Infection in dogs most commonly results in acute renal failure, although hepatic involvement may occur in 20% to 35% of cases.[3,17] It has been suggested that infection in young animals and infection with serovars *L. icterohaemorrhagiae* and *L. pomona* are more likely to result in hepatic involvement.[18] Affected dogs may show acute hepatitis or develop CH with subclinical acute infection. Although cats are generally resistant to leptospirosis, experimental infection with *L. pomona* has caused hepatic lesions in this species.[3] Patients with hepatic involvement will show elevated levels of hepatic enzymes (ALT, AST, ALP), although ALP is often most severely affected.

Hyperbilirubinemia and signs of hepatic failure may occur. Diagnosis of leptospirosis is usually based on clinical suspicion due to renal and hepatic involvement combined with serologic evidence of infection. However, antibody titers may be negative during the first week of infection, and antibody production may persist for only 2 to 6 weeks.[3] Suspected patients with negative antibody titers and a short duration of illness should be treated as though they have leptospirosis, and antibody titers should be repeated in 2 weeks. Histopathologic changes in the liver of affected animals may include coagulative necrosis and infiltration of lymphocytes and plasma cells with lesser numbers of neutrophils and macrophages. Organisms may be identified in biopsy specimens with silver staining, but this is very insensitive. Molecular techniques such as polymerase chain reaction (PCR) are likely to make this diagnosis less challenging in the future. Optimal treatment includes penicillin to eliminate the leptospiremic stage, followed by doxycycline or enrofloxacin to eliminate the carrier state. (NOTE: the use of enrofloxacin in dogs that cannot tolerate doxycycline has not been well studied.) Prognosis is typically good, but patients often require intensive supportive care, including hemodialysis in animals with oliguric or anuric renal failure.

126.6.3.2

Bartonellosis

Bartonella henselae and *Bartonella clarridgeiae* have been identified as causes of hepatic disease in dogs.[19] These arthropod-transmitted bacteria are the etiologic agents of cat-scratch disease in humans and have been isolated from approximately 30% of healthy cats.[20] Clinical findings are similar to those of dogs with other causes of hepatitis. Histologic examination of hepatic tissue from dogs with *B. henselae* infection has revealed peliosis hepatis[21] and granulomatous hepatitis,[19] both of which have been described in infected humans. Diagnosis was made via identification of *Bartonella* DNA using PCR techniques on hepatic biopsy specimens. This is the preferred method of diagnosis because serologic assays impart information only regarding exposure and granulomatous hepatitis may be caused by other agents. The cause of granulomatous hepatitis in dogs is frequently unknown, although reported causes include fungal infection, mycobacterial infection, dirofilariasis, lymphoma, histiocytosis, and intestinal lymphangiectasia.[22] Azithromycin is the antibiotic of choice for treatment of bartonellosis, although its use in dogs with hepatic disease caused by *Bartonella* spp has not been thoroughly evaluated.

126.6.3.3

Septicemia

An important cause of hepatitis in critically ill dogs and cats is bacterial seeding of the liver secondary to bacteremia or via translocation from the GI tract. Commonly isolated aerobic bacteria include *Staphylococcus* spp, *Streptococcus* spp, and enteric gram-negative organisms. Commonly identified anaerobes include *Bacteroides* spp, *Clostridium* spp, and *Fusobacterium* spp.[3] The diagnosis of bacteremia can be difficult in veterinary patients. Septicemia-induced hepatitis should be suspected in critically ill animals that develop clinicopathologic evidence of hepatic disease while hospitalized, especially those in which bacterial infection or severe GI disease have been documented. Treatment with broad-spectrum antimicrobials (pending sensitivity testing), along with aggressive supportive care, are vital to a successful outcome. 550 551

126.6.4

Drugs and Toxins

The main histologic lesion associated with toxic hepatic injury is diffuse centrilobular necrosis. Depending on the temporal relationship between toxin ingestion and tissue biopsy, necrosis may be accompanied by apoptosis or inflammation. Lymphocytic or plasmacytic cellular infiltrates may occur later in the course of disease and have been described commonly with amiodarone,[2] carprofen,[2] and lomustine[23] intoxications. Phenobarbital, primidone, and phenytoin may cause CH that can progress to cirrhosis with prolonged use. Several other drugs reported to cause hepatitis are noted in Box 126-1, but this is by no means an exhaustive list. Treatment involves removal of the offending agent and aggressive supportive care. S-Adenosylmethionine (SAMe) (20 mg/kg PO q24h) has been effective in treating acetaminophen toxicity.[24,25] Although its efficacy against other forms of hepatotoxicity has not been evaluated, it is a logical choice for supportive care in animals suffering any hepatotoxic insult, mainly because of its ability to increase hepatic glutathione levels.

126.7 SUGGESTED FURTHER READING*

SA Center: Acute hepatic injury: Hepatic necrosis and fulminant hepatic failure. In WG Guilford, SA Center, DR Strombeck, DA Williams, DJ Meyer (Eds.): *Strombeck's small animal gastroenterology*. ed 3, 1996, Saunders, Philadelphia, *An excellent review chapter. Although from an older text, most information current. Gives information regarding several causes of acute hepatitis*.

SA Center: Chronic hepatitis, cirrhosis, breed-specific hepatopathies, copper storage hepatopathy, suppurative hepatitis, granulomatous hepatitis, and idiopathic hepatic fibrosis. In WG Guilford, SA Center, DR Strombeck, DA Williams, DJ Meyer (Eds.): *Strombeck's small animal gastroenterology*. ed 3, 1996, Saunders, Philadelphia, *Another excellent review from this older text discussing the causes of CH in dogs and cats in great detail*.

JM Gagne, PJ Armstrong, DJ Weiss, et al.: Clinical features of inflammatory liver disease in cats: 41 cases (1983-1993). *J Am Vet Med Assoc*. **214**, 1999, 513, *A retrospective study describing the clinical signs and clinicopathologic findings in cats with inflammatory liver disease. Diseases classified as acute cholangiohepatitis, chronic cholangiohepatitis, or LPH*.

TN Gillespie, RJ Washabau, MH Goldschmidt, et al.: Detection of *Bartonella henselae* and *Bartonella clarridgeiae* DNA in hepatic specimens from two dogs with hepatic disease. *J Am Vet Med Assoc*. **222**, 2003, 47, *A case series describing two cases of canine hepatic disease where* Bartonella *species were isolated from hepatic tissue via polymerase chain reaction*.

SE Johnson: Chronic hepatic disorders. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, St Louis, *An excellent review of workup and treatment for animals with chronic hepatic disorders containing particularly useful information regarding canine CH*.

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* See the CD-ROM for a complete list of references

127 Chapter 127 Hepatic Failure

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127.1 KEY POINTS

- Hepatic failure is a devastating syndrome, holding a universally poor prognosis.
- A prompt diagnosis, halting disease progression, and supportive therapy while the hepatocytes regenerate are the hallmarks to survival.
- Hepatic encephalopathy and coagulopathy are challenging clinical consequences of fulminant hepatic failure.
- Therapy is aimed at supporting the liver parenchyma and the consequences of its dysfunction, minimizing signs of encephalopathy and treating the underlying pathology, allowing the regenerative capacity of the liver to prevail.

127.2 INTRODUCTION

Liver failure, also referred to as *fulminant hepatic failure*(FHF), is the ultimate common pathway of severe hepatocyte injury, regardless of the cause.[1-3] This condition can manifest as an acute (acute liver failure [ALF]) or chronic (chronic liver failure [CLF]) process. The loss of hepatic function leads to a spectrum of metabolic derangements. FHF is commonly defined by the onset of hepatic encephalopathy (HE) and coagulopathy. Other complications associated with FHF include gastrointestinal (GI) ulceration, bacterial sepsis, cardiopulmonary dysfunction, and ascites. Before the development of hepatic transplantation, humans with FHF had a mortality rate greater than 90%.[1,2] The liver is capable of regenerating 75% of its functional capacity in only a few weeks if the disease process is interrupted and therapy and supportive care are provided.

Common causes of liver disease that can result in FHF in dogs and cats are listed in Table 127-1.[4-6]

127.3 PATHOPHYSIOLOGY

The histologic changes in the liver of patients with ALF or CLF are variable, depending on the underlying disease process. Acute causes of liver disease are likely to display hepatocellular necrosis as the main lesion. Fat accumulation or hepatocellular drop-out may also be noted. Although a chronically diseased liver may also demonstrate hepatocellular necrosis, fibrosis and hyperplasia of ductal structures are often present.

All patients with FHF display common physiologic features, regardless of the cause. These include hypotension, poor oxygen uptake by muscle and peripheral tissues with associated lactic acidosis, electrolyte alterations, HE, and coagulopathy. Over time, dysfunction of multiple organ systems can occur. In humans renal failure is a common sequela to liver failure (hepatorenal syndrome),[7] although this has rarely been described in veterinary patients.[5]

127.3.1 Hepatic Encephalopathy

HE, the hallmark feature of FHF, is a neuropsychiatric syndrome involving a gamut of neurologic abnormalities. The pathogenesis of HE is incompletely understood in both veterinary and human medicine. HE occurs when more than 70% of hepatic function is lost.[2,4,8-11] Multiple aspects of central nervous system (CNS) metabolism have been implicated in the pathophysiology of HE, and over 20 different compounds can be found in increased concentrations in the circulation when liver function is impaired (Table 127-2).[4,8,9,11,12] ALF may result in a form of HE that leads to cerebral edema, increased intracranial pressure, and possible herniation of the brain.[8,9] Edema is described in up to 80% of humans with FHF, and 33% of those patients develop fatal herniation.[3,8,9] It is theorized that combinations of synergistic events and complex metabolic derangements occur in animals or humans with hepatic insufficiency and are responsible for the variable neurologic signs seen. Contributing factors include systemic toxins (see Table 127-2), metabolic derangements (hypoglycemia, dehydration, azotemia, hypokalemia, hyponatremia alkalemia), ingestion of a high-protein diet, GI ulceration, stored red blood cell transfusions constipation, and drug therapy (sedatives, analgesics, benzodiazepines, antihistamines). These factors, in addition to altered permeability of the blood-brain barrier, will impair cerebral function in variable ways[4,8,9] (see Chapter 103, Hepatoencephalopathy).

127.3.2 Coagulation Disorders

Coagulation abnormalities that develop in patients with liver failure are multifactorial, depending on the interactions of the procoagulant, anticoagulant, and fibrinolytic systems. Spontaneous hemorrhage is uncommon. Hemorrhagic complications are usually induced by associated factors such as GI ulceration, invasive procedures (aspiration or biopsy), or other concurrent medical problems. Suggested causes of coagulopathy in patients with liver failure include decreased factor synthesis, increased factor utilization, increased fibrinolysis and tissue thromboplastin release, synthesis of abnormal coagulants (dysfibrinogenemia), decreased platelet function and numbers, vitamin K deficiency (particularly with bile duct obstruction), and increased production of anticoagulants.[4,13]

127.3.3 Other

In addition to an altered mentation and coagulation disorders, FHF has been associated with an increased susceptibility to infection, hypotension, pulmonary abnormalities, acid-base disturbances, renal dysfunction, and 552 portal hypertension, most of 553 which have been described in human patients. Bacterial infection occurs in 80% of human patients.[1,3] Substances have been isolated that inhibit metabolic activity of granulocytic cells, cell adhesion, and chemotaxis.[1,3,4,13] Decreased hepatic synthesis of plasma complement also contributes to infection. Kupffer cells show reduced phagocytic ability, thus allowing pathogens to translocate from the GI tract into the systemic circulation. Hypotension is seen in most humans with FHF, possibly due to systemic vasodilation. This is likely a centrally mediated phenomenon that may be linked to systemic infection and cytokine release, cerebral edema, or circulating toxins. Approximately 33% of humans with FHF develop pulmonary edema. Altered permeability of pulmonary capillaries leading to vascular leak syndromes and vasodilation has been implicated in the development of edema. Changes in capillary permeability can be induced by endotoxemia and this subsequently promotes vascular leakage.[1,3]

Table 127-1 Etiology of Fulminant Hepatic Failure[4–6]

	Dog	Cat
Infectious agents	Canine adenovirus-1 Acidophil cell hepatitis virus Canine herpes virus Clostridiosis Bartonellosis Leptospirosis Liver abscess Tularemia Hepatozoonosis *Rickettsia rickettsii* Histoplasmosis Coccidiomycosis Blastomycosis Leishmaniasis Toxoplasmosis *Dirofilaria immitis* *Ehrlichia canis*	Feline infectious peritonitis Clostridiosis Liver abscesses Histoplasmosis Cryptococcosis Toxoplasmosis Liver flukes
Drugs	Acetaminophen Aspirin Phenobarbital Phenytoin Carprofen Tetracycline Macrolides Trimethoprim-sulfa Griseofulvin Thiacetarsamide Ketoconazole, itraconazole Halothane	Acetaminophen Aspirin Diazepam Halothane Griseofulvin Ketoconazole, itraconazole Methimazole Methotrexate Phenobarbital Phenytoin
Chemical agents and toxins	Industrial solvents Plants (sago palm) Envenomation Heavy metals (copper, iron) Mushrooms *(Amanita phalloides)* Aflatoxins Blue-green algae Cycad seeds Carbon tetrachloride Dimethylnitrosamine Zinc phosphide	Same as for dogs
Miscellaneous	Chronic hepatitis, cirrhosis Idiopathic Copper storage disease Leptospirosis induced Idiosyncratic drug reaction Lobular dissecting hepatitis Granulomatous hepatitis Hepatic amyloidosis (Chinese Shar Pei) Hepatic neoplasia (primary or metastatic disease) Portosystemic shunting Portal venous hypoplasia/microvascular dysplasia (Yorkshire Terrier and Cairn Terrier)	Feline hepatic lipidosis Inflammatory bowel disease Pancreatitis Cholangitis, cholangiohepatitis Septicemia, endotoxemia Hemolytic anemia Neoplasia (lymphoma, mastocytosis) Metastasis Amyloidosis (Abyssinian, Oriental, and Siamese cats)
Traumatic, thermal, hypoxic	Diaphragmatic hernia Shock Liver torsion Heat stroke Massive ischemia	Same as for dogs

Tissue oxygen extraction decreases in patients with FHF, resulting in tissue hypoxia and the development of lactic acidosis. Hypoxemia, which can occur with pulmonary edema, further encourages cerebral dysfunction in patients with HE, accelerating cerebral hypotension and edema. Respiratory distress or arrest, of central origin or secondary to muscle weakness, is a complication that requires mechanical ventilatory support.[1,13] The development of renal failure has been well described in humans, and rarely suggested in dogs.[5] Hypovolemia and hypotension, secondary to FHF and vasodilation, can diminish renal blood flow and glomerular filtration rate.[1-3] Some hepatotoxins (nonsteroidal drugs) and infectious agents (leptospirosis, feline infectious peritonitis) also cause renal tubular or glomerular injury. Portal hypertension secondary to cirrhosis is a common sequela in patients with CLF. It is also noted in some patients with ALF and holds a poor prognosis. Massive sinusoidal collapse can block intrahepatic flow and cause portal pressure elevations. This may lead to severe congestion of the splanchnic vasculature, exacerbating GI bleeding and diarrhea.[3-5]

Table 127-2 Toxins Implicated in Hepatic Encephalopathy[4,6,8-12]

Toxins	**Mechanisms Suggested in the Literature**
Ammonia	Increases brain tryptophan and glutamine levels Brain edema Decreases ATP availability Increases excitability Increases glycolysis Decreases microsomal Na,K^+-ATPase in brain
Decreased α-ketoglutaramate	Diversion from Krebs cycle for ammonia detoxification Decreases ATP availability
Glutamine	Alters blood-brain barrier amino acid transport
Aromatic amino acids	Decreases dopa neurotransmitter synthesis Alters neuroreceptors Increases production of false neurotransmitters
Short chain fatty acids	Decreases microsomal Na,K^+-ATPase in brain Uncouple oxidative phosphorylation Impairs oxygen utilization Displaces tryptophan from albumin, increasing free tryptophan Increases free tryptophan
False Neurotransmitters	
Tyrosine → octopamine	Impairs norepinephrine action
Phenylalanine → phenylethylamine	Impairs norepinephrine action
Methionine → mercaptans	Synergistic with ammonia and short chain fatty acids Decreases ammonia detoxification in brain urea cycle GIT derived (*fetor hepaticus* [breath odor in HE]) Decreases microsomal Na,K^+-ATPase
Tryptophan	Directly neurotoxic Increases serotonin Neuroinhibition
Phenol (from phenylalanine and tyrosine)	Synergistic with other toxins Decreases cellular enzymes Neurotoxic and hepatotoxic
Bile acids	Membrane cytolytic effects alter cell membrane permeability Blood-brain barrier more permeable to other HE toxins Impairs cellular metabolism due to cytotoxicity
GABA	Neural inhibition: hyperpolarize neuronal membrane Increases blood-brain barrier permeability to GABA
Endogenous benzodiazepines	Neural inhibition: hyperpolarize neuronal membrane

ATP, Adenosine triphosphate; *GABA*, γ-aminobutyric acid; *GIT,* gastrointestinal tract; *HE,* hepatic encephalopathy; *Na,K^+-ATPase,* sodium-potassium adenosine triphosphatase.

127.4 CLINICAL SIGNS

Most of the clinical signs seen in dogs and cats with hepatic failure are nonspecific, including anorexia, vomiting, diarrhea, weight loss, and dehydration. Icterus of the mucous membranes, sclerae, hard palate, and skin is a common clinical manifestation. This can be due to either prehepatic (hemolysis), hepatic (intrinsic hepatic injury), and/or posthepatic (functional or mechanical bile duct obstruction) causes. Polyuria and polydipsia are also common findings, which may be secondary to failure of the liver to produce urea, resulting in defective renal medullary concentrating ability and a decreased release and/or responsiveness of the renal collecting ducts to antidiuretic hormone (ADH). Additionally, the central effects of hepatotoxins may cause primary polydipsia. Clinical signs associated with HE include behavioral changes, ataxia, blindness, circling, head pressing, panting, pacing, seizures, coma, and ptyalism (especially cats). The clinical manifestations of HE range from minimal behavior and motor activity changes to overt deterioration of mental function, decreased consciousness, coma, and seizure activity. Bleeding diatheses, melena (due to gastroduodenal ulceration), and/or ascites (due to portal hypertension or hypoalbuminemia) are also common findings.

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127.5 DIAGNOSIS

Fulminant hepatic failure is diagnosed when a patient shows signs of HE, changes in the liver function parameters, evidence of coagulopathy, and associated historical and physical examination findings. Hematologic abnormalities may include the presence of target cells, acanthocytes, and anisocytosis. A nonregenerative anemia may be noted in association with chronic disease, chronic GI bleeding, or portosystemic and microvascular shunting. A regenerative anemia may present secondary to blood loss from gastroduodenal ulceration. Leukocytosis or leukopenia may be noted with primary or secondary infectious causes, depending on the agent and severity of infection. A consumptive thrombocytopenia may occur in animals that develop disseminated intravascular coagulation.

Serum biochemical analysis will reveal elevated activities of hepatic enzymes in most cases. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are found in the cytosol of hepatocytes and leak from the cell after disruption of the cell membrane. ALT is the more liver specific of these enzymes and has a short half-life (24 to 60 hours).[4,6,14,15] AST is present in many tissues (liver, muscle, red blood cells) and has a shorter half-life than ALT. ALP has many clinically significant isoenzymes (bone, liver, and steroid induced [in the dog only]). The hepatic isoenzyme is located on the membranes of hepatocyte canalicular cells and biliary epithelial cells. Its activity increases in association with cholestatic disease. ALP has a very short half-life in cats, making any elevation suggestive of active liver disease. Gamma-glutamyltransferase (GGT) is also found in many tissues, although most of the biochemically measured enzyme is located on membranes of hepatocyte canalicular cells and biliary epithelial cells. GGT is very useful in the diagnosis of cholestatic disease and is more specific and less sensitive than ALP (particularly in feline patients). The presence of normal or only mildly elevated liver enzyme activity does not eliminate FHF as a possible diagnosis, because animals with end-stage hepatic failure or portosystemic vascular anomalies may have normal enzyme activity levels.

Serum biochemical analysis may also reveal hyperbilirubinemia in animals with FHF. Bilirubin is one of the breakdown metabolites of hemoglobin, myoglobin, and cytochromes. With significant cholestasis, bile duct obstruction, or canalicular membrane disruption, bilirubin will escape into the systemic circulation, resulting in hyperbilirubinemia and the typical icteric appearance to the skin, mucous membranes, and organs (visible when values are >2.3 and 3.3 mg/dl).[6,14,15]

The liver function parameters that are classically noted when hepatic failure is present include hypoalbuminemia, hypocholesterolemia, hypoglycemia, and decreased blood urea nitrogen levels (BUN). Albumin is produced only in the liver, representing approximately 25% of all protein synthesized by the liver. Altered albumin synthesis is not detected until more than 66% to 80% of liver function is lost.[15] Because of its long half-life (8 days in dogs and cats), hypoalbuminemia is a hallmark of chronic liver dysfunction (although concomitant disease processes may also contribute). Cholesterol is synthesized in many tissues, although up to 50% of its synthesis occurs in the liver. In FHF, hypocholesterolemia is commonly observed. With extrahepatic bile duct obstruction or pancreatitis, cholesterol elimination is altered and hypercholesterolemia can develop. Because the liver helps to maintain glucose homeostasis via gluconeogenesis and glycogenolysis, hypoglycemia may develop when less than 30% of normal hepatic function is present.[4,6]

Urine sediment examination may show ammonium biurate or urate crystals, particularly in animals with portosystemic vascular anomalies. Dogs have the ability to produce and conjugate bilirubin in their renal tubules, accounting for a very small amount of bilirubinuria in a healthy state (males more than females). Cats, on the other hand, do not have this ability and have a threshold that is 9 times higher than that of dogs to reabsorb bilirubin rather than eliminate it in the urine.[4,14] Hence, bilirubinuria in the cat is always inappropriate and indicative of abnormal bilirubin metabolism.

Additional testing may be performed to assess hepatic function. Coagulopathies are classically seen in animals with FHF. Prolongation of the activated partial thromboplastin time (aPTT), prothrombin time (PT), activated clotting time (ACT), and buccal mucosal bleeding time (BMBT) may be observed. Increased fasting and postprandial serum bile acid levels are highly indicative of hepatic dysfunction, and are classically seen in animals with FHF. They may also play a role in inciting inflammatory liver disease.[4,6] Plasma fasting ammonia level, 6-hour postprandial ammonia level, and/or ammonia tolerance testing are sensitive tests of liver function. The ammonia tolerance test is contraindicated in animals with encephalopathy and may precipitate seizure activity.[4-6,14]

Electrolyte abnormalities may also be seen in animals with FHF. Hypokalemia may develop as a result of inadequate intake, vomiting, or potassium-wasting diuretics. Centrally induced hyperventilation and respiratory alkalosis may encourage renal potassium excretion, worsening the hypokalemia. A decrease in potassium levels may exacerbate HE. In addition, hypocapnia results in a shift of intracellular carbon dioxide into the extracellular space, raising intracellular pH and accelerating the utilization of phosphate to phosphorylate glucose, with resulting hypophosphatemia.

Diagnostic imaging is often useful in determining the underlying cause of FHF. Abdominal radiographs are useful for determining liver size and contour, identifying mass lesions, and evaluating abdominal detail, which may be decreased in animals with ascites. Abdominal ultrasonography is valuable for the evaluation of hepatic parenchymal architecture, the biliary tract, and vascular structures. It can also help to guide diagnostic sampling procedures, when indicated.

Ultimately, cytologic or histologic evaluation will be necessary to determine the underlying cause of FHF. Fine-needle aspiration cytology is useful for diagnosing infiltrative neoplasia such as lymphoma, but gives little information about the hepatic parenchymal changes needed for a definitive diagnosis of the inflammatory/infectious, necrotic, fibrosing, and microvascular diseases. Aspiration is very insensitive in making a definitive diagnosis.[16] Histopathologic evaluation of liver tissue is more useful and should be obtained whenever possible. Liver biopsies can be performed with either ultrasound guidance, laparoscopically, or surgically. In humans, a transjugular approach under fluoroscopic guidance is commonly used, particularly in patients with coagulopathies, to avoid penetrating the hepatic capsule and causing third-space bleeding.[1] A blood type and coagulation profile

should be obtained before liver biopsy in all patients. A small amount of liver tissue should be harbored so that 555
further testing can be performed if indicated by histopathology, such as aerobic and anaerobic culture, copper 556
analysis (dogs), or polymerase chain reaction (PCR) testing for certain infectious agents.

127.6 THERAPY

Successful management of patients with FHF requires treatment of the underlying liver disease, symptomatic therapy aimed at the complications of hepatic failure, and routine supportive care. Fortunately, hepatocytes have an impressive ability to regenerate if given appropriate support and time. Treatment of the primary disease process, if possible, is of utmost importance. However, a discussion of the treatment recommendations for specific liver diseases of dogs and cats is beyond the scope of this chapter. Symptomatic therapy for the complications of liver failure is similar, regardless of the underlying cause. Supportive care is required to maintain the normal physiologic functions of the animal while the liver recovers from the insult (Table 127-3).

Table 127-3 Therapies for Fulminant Hepatic Failure

Symptom	Therapy
Bacterial translocation	Cleansing enemas with warm water or 30% lactulose solution at 5 to 10 ml/kg (see Chapter 102, Tetanus)
	Antibiotics
	Metronidazole 7.5 mg/kg IV or PO q12h
	Ampicillin 22 mg/kg IV q 6h
	Neomycin 22 mg/kg PO q 8h (avoid if any evidence of intestinal bleeding, ulcerations, or renal failure)
Gastrointestinal ulceration	**Antacid**[20]
	Famotidine 0.5 to 1 mg/kg/day IV or PO
	Omeprazole 0.5 to 1 mg/kg/day PO q 12h
	Esomeprazole 0.5 mg/kg IV q 12-24h
	Misoprostol 2 to 3 μg/kg PO q 8-12h
	Protectant
	Sucralfate 1 g/25 kg PO q 8h; separate from antacid by at least 2 hours
	Other
	Correct coagulopathy
Coagulopathy	Fresh frozen plasma 10 to 15 ml/kg over 2 to 3 hours
	Vitamin K_1 1.5 to 2 mg/kg SC or IM q 12h for 3 doses, then q 24h
Control seizures	Avoid benzodiazepines (this is controversial)
	Consider propofol 0.5 to 1 mg/kg IV bolus + IV CRI at 0.05 to 0.1 mg/kg/min
	or
	Phenobarbital (16 mg/kg IV, divided into 4 doses over 12 to 24 hr)
	or
	Potassium bromide, sodium bromide loading (see Chapter 102, Tetanus)
Decrease cerebral edema	Mannitol 0.5 to 1 g/kg IV over 20 to 30 min
Hepatoprotective therapy	SAMe (Denosyl) 17 to 22 mg/kg PO q 24h
	Ursodeoxycholic acid (Actigall) 10 to 15 mg/kg PO q24h
	Vitamin E 15 IU/kg PO q 24h
	Milk thistle 8 to 20 mg/kg PO divided q 8h
	L-Carnitine 250 to 500 mg/cat PO q24h
	Vitamin B complex 1 ml/L of IV fluids

Antifibrotic therapy	D-Penicillamine 10 to 15 mg/kg PO q12h
	Colchicine 0.03 mg/kg PO q24h
	Prednisone or prednisolone 1 mg/kg PO q24h
Nutritional support	Moderate protein restriction: 14% to 17% dogs and 30% to 35% cats (on a dry matter basis)
	Diary or vegetable proteins
	Vitamin B supplementation
	Multivitamin supplementation

CRI, Constant rate infusion; *IM,* intramuscular; *IV,* intravenous; *PO,* per os; *SAMe,* S-adenosyl-L-methionine; *SC,* subcutaneously.

Animals that present with or develop focal or generalized seizure activity require immediate anticonvulsant therapy (see Table 127-3 and Chapters 98, 103 and 186, Seizures and Status Epilepticus, Hepatoencephalopathy, and Anticonvulsants, respectively). Propofol (0.5 to 1 mg/kg IV bolus, then 0.05 to 0.1 mg/kg/min constant rate infusion) is generally recommended for rapid control of seizures due to hepatoencephalopathy. Endotracheal intubation should be performed in patients that are hypoventilating, because hypercapnia will further increase intracranial pressure (and to protect the airway from aspiration). Mannitol therapy may also prove beneficial if cerebral edema is present (0.25 to 1 g/kg IV over 20 to 30 minutes), especially considering the frequency of cerebral edema with associated herniation in humans.[1–3]

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The use of diazepam in the treatment of seizures in animals with HE is controversial. GABA and its receptors are implicated in the pathogenesis of HE and the use of a benzodiazepine antagonist, such as flumazenil, has been shown to be of benefit in humans with HE-induced comas.[8,9] Flumazenil has not yet been evaluated in veterinary patients, however.

Symptomatic therapy for patients with HE may include withholding food, cleansing enemas with warm water and/or lactulose, oral lactulose therapy, and antibiotic therapy.[4–6,10] Antibiotics such as metronidazole, neomycin, and ampicillin will decrease GI bacterial numbers, decreasing ammonia production. Metronidazole and ampicillin also help decrease the risk of bacterial translocation and systemic bacterial infections. However, neurotoxicity from metronidazole therapy may occur more commonly in animals with hepatic disease. Rifaximin is another commonly used antibiotic for the treatment of HE in humans, but its use in small animals is limited at this time. Symptomatic therapy is necessary for bleeding patients. Those with gastric ulceration should be treated with acid-receptor blockade (histamine-2 blocker, proton pump inhibitor, prostaglandin analog) and sucralfate (see Chapter 181, Gastrointestinal Protectants). Ranitidine may not be a very effective antacid in dogs and its efficacy in cats is unknown.[17] Patients with coagulopathy that have signs of active bleeding should be treated with fresh frozen plasma or fresh whole blood and vitamin K_1 (especially if the coagulopathy is thought to be due to cholestasis and fat malabsorption).[4-6] Patients that are significantly anemic will benefit from packed red blood cell or whole blood transfusions. If there is evidence of HE, fresh whole blood is preferred, because stored blood harbors ammonia (see Chapter 66, Transfusion Medicine).

Ascites and fibrosis may be seen in patients with chronic, severe liver disease. If ascites is due to low oncotic pressure, then synthetic colloidal therapy should be considered (see Chapter 64 Daily Intravenous Fluid Therapy). If the ascites is due to portal hypertension, the use of diuretics and a low-sodium diet should be considered. Spironolactone is the initial diuretic of choice for its aldosterone antagonism and subsequent potassium-sparing effects. Furosemide may be necessary, as well, but should be used with caution, because it may potentiate hypokalemia. A number of drugs theoretically decrease connective tissue formation and may be helpful in patients with hepatic fibrosis. Prednisone, D-penicillamine, and colchicine have been recommended (see Table 127-3).[4-6,15]

Fluid therapy and nutritional support are the cornerstones of supportive therapy. Fluid therapy is indicated to maintain hydration and provide cardiovascular (and occasionally oncotic) support. Lactated Ringer's solution is often avoided because of the need for hepatic conversion of lactate to bicarbonate. Potassium and glucose supplementation is often required. Nutritional management is important in patients with both ALF and CLF, particularly cats with hepatic lipidosis. The diet should be readily digestible, contain a protein source of high biologic value (enough to meet the animal's need, but not to promote HE), supply enough essential fatty acids, maintain palatability, and meet the minimum requirements for vitamins and minerals. Low-protein diets should be avoided unless HE is noted. Milk and vegetable proteins are lower in aromatic amino acids and higher in branched chain amino acids (valine, leucine, isoleucine) than animal proteins and are considered less likely to potentiate HE.[4,6,15] In the patient with FHF, total or partial parenteral nutrition should be considered if enteral intake cannot be tolerated (see Chapter 14, Parenteral Nutrition). If there is no vomiting or regurgitation and temperature and systemic blood pressure are stable, but the patient will not eat voluntarily, a feeding tube should be considered to allow for localized enterocyte nutrition (see Chapter 13, Enteral Nutrition).

Supportive nutraceutical therapy has been recommended for a variety of liver diseases. Drugs in this class include S-adenosylmethionine (SAMe), vitamin E, and milk thistle.[17] SAMe has hepatoprotective, antioxidant, and antiinflammatory properties. It also serves as a precursor to the production of glutathione, which plays a critical role in detoxification of the hepatocyte. Vitamin E is another antioxidant and should be considered to prevent and minimize lipid peroxidation within the hepatocytes. Silymarin is the active extract in milk thistle. There is an abundance of both in vivo animal and in vitro experimental data showing the antioxidant and free radical scavenging properties of silymarin.[18] Specifically, it is shown to inhibit lipid peroxidation of hepatocyte and microsomal membranes. Silymarin increases hepatic glutathione content and appears to retard hepatic collagen formation.[17]

Ursodeoxycholic acid, another hepatoprotective medication, is recommended for the treatment of most types of inflammatory, oxidative, and cholestatic liver disease. It has antiinflammatory, immunomodulatory, and antifibrotic properties, and promotes choleresis and decreases the toxic effects of hydrophobic bile acids on hepatocytes. This medication is contraindicated in patients with biliary duct outflow obstruction until after the obstruction is relieved.

Zinc is an essential trace mineral involved in many metabolic and enzymatic functions of the body and is an important intermediary involved in enhanced ureagenesis, glutathione metabolism, copper chelation, and immune function. Zinc appears to have antifibrotic activities as well. Zinc deficiency occurs in many humans with liver disease and seems to correlate with HE, demonstrating its importance in ureagenesis. Please refer to other sources for further explanation.[17]

127.7

PROGNOSIS

The prognosis for small animal patients with FHF is generally poor. Few published guidelines are established to predict outcome. Some factors suggested to be poor prognostic indicators include PT longer than 100 seconds, very young or very old animals, viral or idiosyncratic drug reaction as the underlying cause, and a markedly increased bilirubin level.[4] When a known hepatotoxin is involved, an antidote can markedly improve survival. Better survival rates are likely attained in an environment where aggressive and intensive supportive therapy is available. Young dogs with HE and FHF from portosystemic shunting hold a fair prognosis if the HE is controlled before surgical or interventional correction.

127.8 FUTURE THERAPIES

Humans with severe HE are placed immediately on a liver transplant list, which may be an option for veterinary patients in the future. Substitution of hepatocytes in various forms of artificial liver support has been promoted over the past 10 years in human medicine. A multicenter randomized trial of a bioartificial liver (while awaiting transplantation) showed no benefit over traditional therapy in overall outcome, although more advanced equipment is showing great promise. Research is still avid in this area and something similar may be seen in the future in veterinary medicine.[1–3,8,9,19] 557 558

Overall, FHF is a severe, life-threatening disease that holds a poor prognosis. With aggressive intensive care, avid supportive therapy, and early diagnosis, the regenerative capacity of the liver will improve, as will the outcome.

127.9 SUGGESTED FURTHER READING*

D Shawcross, R Jalan: Dispelling myths in the treatment of hepatic encephalopathy. *Lancet*. **365**, 2005, 431, *An excellent review of medical management for HE, discussing the physiology behind the various therapies we use*.

J Taboada: Hepatic pathophysiology. In Proceedings of the International Veterinary Emergency and Critical Care Symposium, September 9–13, 2003, LA, New Orleans, *A good discussion of the pathophysiology of hepatic disease in dogs and cats*.

CR Webster: History, clinical signs, and physical findings in hepatobiliary disease. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, St Louis, *A good chapter for the discussion of basic pathophysiology and clinical changes seen in veterinary patients with liver disease*.

MD Willard, DC Twedt: Gastrointestinal, pancreatic, hepatic disorders. In MD Willard, H Tvedten, GH Turnwald (Eds.): *Small animal clinical diagnosis by laboratory methods*. ed 4, 2004, Saunders, Philadelphia, *A veterinary textbook that provides some informative details on biochemical testing in animals*.

* See the CD-ROM for a complete list of references

128 Chapter 128 Gastroenteritis

Tara K. Trotman, VMD, DACVIM

128.1 KEY POINTS

- Clinical signs of acute gastroenteritis typically involve vomiting, diarrhea, and partial or complete anorexia.
- Physical examination findings are often nonspecific but may include abdominal discomfort, dehydration, and hypovolemia.
- There are a wide variety of causes for gastroenteritis, and determination of an underlying cause is often not possible. However, a minimum database should include packed cell volume, total protein, Azostik, blood glucose, acid-base, and electrolyte status.
- Supportive care is the mainstay of therapy if an underlying cause is not found. Prognosis for most dogs and cats with gastroenteritis is excellent.

128.2 INTRODUCTION

Gastroenteritis is a broad term used to indicate inflammation of both the stomach and the intestinal tract. It is a common cause for acute-onset vomiting, anorexia, and diarrhea in both dogs and cats, but should be differentiated from other problems that may cause similar clinical signs such as pancreatitis, hepatitis, and intestinal obstruction (see additional chapters under the textbook section Intraabdominal Disorders).[1] Inflammation in the alimentary tract can be due to a wide variety of underlying causes, including dietary indiscretion, infectious organisms, toxins, immune dysregulation, and metabolic disorders, and may occur in both dogs and cats. A thorough history and physical examination may aid in uncovering an underlying cause, but often a specific cause is not identified. In most cases, supportive therapy, including appropriate fluid support, dietary modification, antiemetics, and gastric protectant agents, are sufficient for resolution of clinical signs. However, in severe cases acute decompensation can occur. This is usually secondary to volume depletion, fluid losses, and acid-base disturbances that occur because the intestinal tract cannot perform its normal hemostatic functions.

128.3 ANATOMY AND PHYSIOLOGY

The stomach is the compartment between the esophagus and small intestine that functions as both a storage reservoir for food and a vessel for mixing and grinding food into smaller components that then enter the small intestine.[2] The stomach, is made up of muscular layers, glandular portions, and a mucosal barrier. The muscular layers serve to grind food into smaller particles and move it forward into the small intestine through the pyloric sphincter. Of equal importance are the glandular portions of the stomach, which include parietal cells (for secretion of hydrochloric acid), chief cells (for secretion of pepsinogen), and mucous-producing cells (which also secrete bicarbonate). The gastric mucosal barrier is able to keep hydrochloric acid and digestive enzymes within the lumen, and it prevents loss of plasma constituents into the stomach.[2] Once the food particles are ground into small enough components, they pass through the pyloric sphincter into the beginning of the small intestine, known as the *duodenum*.

The small intestine of cats and dogs functions in both digestion and absorption of food and its nutrients, and is divided arbitrarily into the duodenum, jejunum, and ileum.[3] The mucosa of the small intestine is involved in both secretory and absorptive functions and contains a single layer of epithelial cells called *enterocytes*. The mucosa along the length of the small intestine is formed into villi, which are fingerlike projections into the intestinal lumen that enlarge the surface of the small intestine. Microvilli then form the “brush border” to increase the surface area even more for digestion and absorption of nutrients. Enzymes found in this brush border aid in digestion of larger food molecules into smaller, more readily absorbable particles. Absorption may occur via specific transport mechanisms or by pinocytosis. The epithelial cells are also involved with absorption and secretion of electrolytes and water.[3] Enterocytes are connected to each other by tight junctions, limiting absorption between cells, as well as preventing backflow of nutrients from the interstitium into the intestine. The life span of these enterocytes is likely somewhere between 2 and 5 days, and they start at the crypt (base of the villus) and migrate toward the intestinal lumen where they are shed. A healthy, intact mucosal lining is important for the integrity of the intestine. Any type of inflammation that disrupts this layer can lead to significant intestinal disease.[4] It is also important to remember that the gastrointestinal (GI) tract absorbs about 99% of the fluid presented to it; therefore any damage to it can cause significant alterations in acid-base and fluid balances.[5]

128.4 HISTORY AND CLINICAL SIGNS

A thorough history is extremely important in identifying an underlying cause for gastroenteritis. Questions may be related to the patient's current diet, recent change in diet, and exposure to unusual food, foreign materials, garbage, or toxins. It is also important to find out about the patient's environment, including exposure to other animals, and if other exposed animals have similar signs or a history of similar signs. Vaccination status, deworming history, and medication use are also important.

Clinical signs of gastroenteritis are often similar regardless of the underlying cause. Vomiting, diarrhea, and anorexia are most common, and certain combinations of these signs may make one cause more or less likely than another. Severe inflammation or ulceration, depending on the cause, can lead to hematemesis or melena.

Physical examination is often unrewarding in terms of helping to find an underlying cause. Patients may have varying degrees of dehydration, as well as abdominal pain. In severe cases, such as those animals with hemorrhagic gastroenteritis (HGE) or parvoviral enteritis, patients may have signs of hypovolemia and shock due to the severe fluid losses and acid-base disturbances.

128.5 ETIOLOGIES

128.5.1 Infectious Gastroenteritis

A variety of infectious agents can affect the GI tract. Viruses, bacteria, parasites, and fungi have all been shown to cause gastroenteritis of varying severity. The descriptions in the text are limited to the most common. Please see Box 128-1 for a more complete list of potential infectious causes of gastroenteritis.

128.5.2 Viral Enteritis

Canine parvovirus-2 (CPV-2) is one of the most common infectious diseases in dogs and may be characterized by severe enteritis, vomiting, hemorrhagic diarrhea, and shock.[4] The pathophysiology and treatment of CPV-2 are discussed in Chapter 112, Canine Parvovirus Infection. Other viral diseases that can lead to severe GI inflammation include coronavirus and rotavirus infection, although clinical manifestations of these viral diseases are thought to be milder than those of CPV-2, likely because they affect the tips of the villi, whereas CPV-2 affects the crypts.[6] Feline panleukopenia, also caused by a parvovirus, can cause similar signs of severe gastroenteritis.

128.5.3 Bacterial Enteritis

The bacterial organisms most commonly associated with acute gastroenteritis in dogs and cats include *Clostridium perfringens and C. difficile, Campylobacter jejuni* and *C. upsaliensis, Salmonella* spp, *Helicobacter* spp, and enterotoxigenic *E. coli.* [7-10] There is still controversy as to whether some of these organisms truly cause clinical disease. Evidence does support the role of *Clostridium* spp in gastroenteritis.[8-9] Evaluation of the roles of these organisms, as well as those of *Campylobacter* and *Helicobacter,* in GI disease of companion animals is ongoing.

128.5.3.1 Box 128-1 Infectious Causes of Gastroenteritis in Dogs and Cats

128.5.3.1.1 Bacterial

Campylobacter spp

Clostridium spp

Escherichia coli

Salmonella spp

Helicobacter spp

128.5.3.1.2 Viral

Parvovirus

Rotavirus

Enteric coronavirus

Feline infectious peritonitis

Canine distemper virus

Feline leukemia virus

Feline immunodeficiency virus

128.5.3.1.3 Fungal, Algal, and Oomycoses

Histoplasmosis

Protothecosis

Pythiosis

128.5.3.1.4 Parasitic

Ascarids *(Toxocara canis, Toxocara cati, Toxascaris leonina)*

Hookworms (*Ancylostoma* spp, *Uncinaria stenocephala*)

Strongyloides stercoralis

Whipworms *(Trichuris vulpis)*

Coccidiosis *(Isospora canis* or *felis, Toxoplasma gondii, Cryptosporidium parvum)*

Giardia

Trichomonas

Balantidium coli

128.5.3.1.5 Rickettsial

Neorickettsia helminthoeca (Salmon poisoning)

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128.5.4 Parasitic Gastroenteritis

Although most dogs and cats with GI parasites have mild clinical signs, ascarids (*Toxocara* spp, *Toxascaris leonina, Ollulanus tricuspis,* and *Physaloptera*), hookworms (*Ancylostoma* spp, *Uncinaria stenocephala*), and whipworms (*Trichuris* spp) can cause significant inflammation, vomiting, and diarrhea. Protozoans that cause canine and feline gastroenteritis include *Giardia,* coccidia, and *Cryptosporidia*.

128.5.5 Fungal Gastroenteritis

Fungal disease can affect the GI tract of both dogs and cats, although the likelihood greatly depends on the geographic locations to which the patient has been exposed. Histoplasmosis is the fungal pathogen that affects the GI tract most commonly and can cause a severe protein-losing enteropathy (PLE). *Pythium* spp, an oomycete, can also cause similar disease.

128.5.6 Hemorrhagic Gastroenteritis

HGE is a disease of unknown etiology. It typically affects young to middle-aged, small breed dogs, and its clinical course usually includes a peracute onset of clinical signs that can progress rapidly to death without appropriate therapy.[7,11] Affected animals are usually previously healthy dogs with no pertinent historical information. The syndrome is characterized by acute onset of bloody diarrhea, often explosive, along with an elevated packed cell volume (PCV) (≥60%).[7,11] Although the etiology remains unknown, it has been suggested that abnormal immune responses to bacteria, bacterial endotoxin, or dietary ingredients may play a role.[12] Although *C. perfringens* has been isolated from cultures of GI contents in dogs with HGE, its exact role in the syndrome has not been determined.

Clinical signs of vomiting and depression, progressing to explosive, bloody diarrhea and anorexia, are classic, and the diarrhea is often described as having the appearance of raspberry jam.[7] Thorough investigation to rule out other causes of hemorrhagic diarrhea such as parvovirus, bacterial infections, or GI parasites should be undertaken before arriving at a diagnosis of HGE. Along with hemoconcentration, there is typically little to no increase in the total protein concentration. The elevated PCV occurs due to hypovolemia or splenic contraction, whereas GI loss of serum proteins or redistribution of body water into the vascular space explains the lack of rise in total protein levels.[7]

Aggressive therapy is warranted in these cases because rapid decompensation may occur. Adequate replacement of fluid volume is essential for these dogs. More specific fluid management can be found in Chapters 64 and 65, Daily Intravenous Fluid Therapy and Shock Fluids and Fluid Challenge, respectively, but general goals are to quickly replace the fluid lost from acute diarrhea and vomiting, and then adjust fluid rates to maintain proper hydration. It is important to remember that the GI tract is a “shock organ” in the dog, and lack of proper perfusion to the gut can lead to worsening GI inflammation, bacterial translocation, sepsis, and disseminated intravascular coagulation.[13,14] Because serum proteins are lost through the intestinal tract, close attention should be paid to the patient's colloid osmotic pressure and colloidal support given when necessary. Although fluid therapy is the mainstay of treatment for HGE, antiemetic drugs may be indicated, as well as antibiotics if bacterial translocation is suspected. With rapid and appropriate therapy, the prognosis for full recovery from HGE is excellent.

128.5.7 Dietary Indiscretion

Gastroenteritis caused by ingestion of toxins (i.e., organophosphates), foreign materials, or garbage is common in dogs, and less so in cats. Some toxins lead directly to inflammation of the GI tract, although ingestion of other foreign materials may lead to direct GI trauma or an osmotic diarrhea secondary to nondigestible substances within the intestinal tract. Ingestion of excessive fatty products may also cause pancreatitis in these animals. Many drugs are associated with vomiting and diarrhea (antibiotics, antineoplastics, anthelminthics), and garbage ingestion can lead to exposure of the intestinal tract to preformed bacterial toxins. Most commonly, dietary indiscretion leads to acute onset of vomiting, diarrhea, and anorexia. History is useful because the owner may be aware that the patient was exposed to a specific toxicant or garbage. Diagnosis is usually presumptive, and treatment involves supportive care such as fluid therapy to maintain hydration, antiemetic drugs, and gastric protectants as needed. Prognosis is excellent, and most animals recover within 24 to 72 hours.

128.5.8 Protein-Losing Enteropathy

PLE is a broad diagnosis that includes any cause of GI disease that results in excessive loss of plasma proteins. The diseases most commonly associated with PLE are severe lymphocytic-plasmacytic, eosinophilic, or granulomatous inflammatory bowel diseases, lymphangiectasia, diffuse GI fungal disease, and diffuse neoplasia such as lymphosarcoma. Some of the aforementioned GI diseases can cause PLE if the inflammation and damage to the intestinal mucosa are severe enough.

The mechanism of protein loss may be related to inflammation or loss of the GI barrier.[15] Protein loss very likely arises because of disruption to the normal enterocyte function, as well as deranged permeability through the tight junctions.[15] Clinical signs of PLE are usually associated with chronic wasting because of the lack of nutrient integration into the body. However, the proteins lost into the intestinal tract can include large proteins such as albumin and antithrombin III, both of which have important roles in homeostasis. Albumin, with a molecular weight of 69,000 daltons, contributes significantly to oncotic pressure. Loss of albumin through the GI tract can lead to reduced colloid osmotic pressure, which often leads to loss of fluid from the intravascular space. Although this is typically a gradual process, it can cause significant changes in the compartmentalization of fluids in the patient, which may require consideration when prescribing fluid therapy. If third spacing has occurred, it may be necessary to use colloidal fluids such as hydroxyethyl starch (Hetastarch) or human albumin, in addition to crystalloids, in order to prevent further intravascular fluid losses. Albumin has additional beneficial effects, such as its antioxidant and antiinflammatory properties.[16]

Antithrombin III plays a critical role in the coagulation and fibrinolytic cascade by inactivating thrombin and other clotting factors. Even a small reduction in antithrombin III levels can cause a large propensity toward thrombosis and thromboembolism. This becomes important in patients with PLE that lose large amounts of 560 protein and are predisposed 561 to developing thromboemboli in various parts of the body, including the pulmonary vessels, portal vein, or cerebral vessels. Therapy for PLE often involves glucocorticoids, which also increase the risk of thromboembolic disease. Therefore anticoagulant or antiplatelet therapy, or both, may be warranted in these cases.

Therapy for PLE is aimed at treating the underlying cause. Animals with diffuse neoplasia such as lymphosarcoma should be treated with chemotherapy, and those with severe inflammatory bowel disease should receive antiinflammatory drugs and a hypoallergenic diet. Lymphangiectasia may be primary or secondary, and administration of a diet low in fat may be more important than feeding a hypoallergenic diet, depending on the degree of inflammation.

128.5.9 Extraintestinal Diseases

Hypoadrenocorticism, liver or kidney disease, acute pancreatitis, and peritonitis are common extraintestinal causes of gastroenteritis in small animals.

128.6 DIAGNOSIS

The extent of diagnostic testing in a dog that presents with signs of acute gastroenteritis depends on factors such as historical information, prior occurrence of similar clinical signs, and stability of the patient. Fecal samples should be evaluated for both parasitic diseases and bacterial infections in most animals with clinical signs of acute gastroenteritis. A culture can be performed in addition to a Gram stain evaluation. Feces should be evaluated at least three times before a negative result is confirmed. Testing for clostridial enterotoxins may include use of a *C. perfringens* enterotoxin enzyme-linked immunosorbent assay (ELISA), or an ELISA that detects *C. difficile* toxins A and B. A *Giardia* antigen test also exists. If parvovirus is suspected, a fecal antigen test (ELISA) should be performed.

Systemic evaluation should include a complete blood count, chemistry screen, and urinalysis. Typically results of these tests are normal and do not aid in determining an underlying cause for the gastroenteritis. However, in certain circumstances such as HGE (in which the PCV is elevated with a normal total protein concentration) and PLE (which causes a decrease in total protein, globulin, albumin, and cholesterol levels), these tests can aid in diagnosis. Electrolytes should be checked regularly to confirm adequate fluid management.

Abdominal radiographs may be unrewarding or may show signs of fluid-filled bowel loops. Radiographs are indicated if a GI obstruction (i.e., foreign body, neoplasia) is suspected. Abdominal ultrasonography is an excellent tool to evaluate all abdominal organs, including the thickness and layering of the stomach and small intestine. These findings may be insensitive and nonspecific, however, and should always be used in conjunction with other diagnostic tests.

If PLE is suspected and biopsies of the stomach and intestine are required, there are two main ways of achieving this. Endoscopy is a noninvasive method for visualizing the esophageal, gastric, and duodenal mucosa, as well as for obtaining small (1.8 to 2.4 mm) biopsy samples. Disadvantages of this method are that the samples are small, and biopsies cannot be performed distal to the duodenum. Ileal samples can be obtained if colonoscopy is performed, but this requires patient preparation (i.e., administration of cleansing enemas), which can cause decompensation in unstable animals resulting from fluid and electrolyte shifts. The other option for obtaining samples requires exploratory laparotomy. This is an excellent method for acquiring full-thickness biopsy samples of multiple areas of the GI tract (and other organs if they are found to be abnormal). The disadvantages are that it is much more invasive, and poor wound healing may be a concern in patients with reduced albumin levels. This has been reported in human surgical patients, as well as canine surgical patients.[17,18] Additionally, diseased gastric and intestinal walls may heal poorly.

The most common clinical signs of gastroenteritis are vomiting, diarrhea, and anorexia. These are common to a variety of diseases; therefore gastroenteritis is often a diagnosis of exclusion. Differential diagnosis might include systemic diseases such as kidney disease, liver disease, hypoadrenocorticism, complicated diabetes mellitus (diabetic ketoacidosis), vestibular disease or other neurologic abnormalities, pancreatitis, pyometra, prostatitis, and peritonitis. Additional primary GI diseases to rule out might include intussusception, foreign body or mass obstruction, infiltrative disease (neoplasia, infectious), or ischemia. It is important to rule out these other disorders, as indicated, to make a diagnosis of gastroenteritis.

128.7 TREATMENT

Most cases of gastroenteritis will respond well to supportive care. Aggressiveness of treatment depends on the severity of clinical signs and the underlying cause. Because the most common clinical signs of gastroenteritis, regardless of underlying cause, are vomiting, diarrhea, and anorexia, dehydration is a common occurrence, and initial therapy should be aimed at addressing the patient's hydration status (see Chapters 64 and 65, Daily Intravenous Fluid Therapy and Shock Fluids and Fluid Challenge, respectively).

Other treatments can be divided into specific therapies or symptomatic treatments. Specific drugs can be used to treat some of the underlying causes of disease. For the most part, drugs used to eradicate many of the infectious causes for gastroenteritis are available. GI parasites may be treated with fenbendazole or other antihelminthic drugs. *Campylobacter* spp have responded well to such drugs as erythromycin, enrofloxacin, and cefoxitin,[19] and *Clostridium* spp may respond to metronidazole or ampicillin.[20] The choice of drug depends on many factors, including patient age and ability to take oral medications. Few antiviral drugs are effective in veterinary medicine; therefore diseases such as parvoviral enteritis are treated supportively. As stated before, the aims of therapy in animals with PLE are to treat the underlying cause, commonly with diet change and antiinflammatory drugs.

Many of the drugs used to treat gastroenteritis are nonspecific. In addition to fluids, many animals will respond well to resting the GI tract by withholding food for 24 to 48 hours. When food is offered, a wet, easily digestible diet is recommended. Addition of GI protectants (see Chapter 181, Gastrointestinal Protectants) or antiemetics (see Chapter 182, Antiemetics), or both, may hasten recovery of the enterocyte damage and give the GI tract time to heal. In cases of severe GI damage, in which bacterial translocation is a concern (especially in puppies with parvoviral enteritis), antibiotics may be indicated. Antibiotic therapy should be aimed at treating the common organisms expected in the intestinal tract and usually consists of antibiotics with good gram-negative and anaerobic coverage.

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128.8 PROGNOSIS

In conclusion, prognosis for animals with mild to moderate gastroenteritis is typically excellent. However, early diagnosis and timely therapy are important for positive outcomes.

128.9 SUGGESTED FURTHER READING*

DK Macintire, S Smith-Carr: Canine parvovirus. Part II. Clinical signs, diagnosis, and treatment. *Comp Cont Educ Pract Vet.* **19**, 1997, 291, *Second part of a two-part review article on canine parvovirus discussing clinically relevant clinical signs, diagnosis, and treatment; an excellent review for anyone wanting to brush up on treatment.*

DL McCaw, JD Hoskins: Canine viral enteritis. In CE Greene (Ed.): *Infectious diseases of the dog and cat.* 2006, Saunders, St Louis, *The "must have" textbook for anyone interested in infectious disease.*

KW Simpson, N Birnbaum: Fluid and electrolyte disturbances in gastrointestinal and pancreatic disease, and Center SA: Fluid, electrolyte, and acid-base disturbances in liver diseases. In SP DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders in small animal practice*. 2006, Saunders, St Louis, *Two chapters that provide important information about electrolyte changes in GI disease and why they occur. An excellent tool to help understand why the intestinal tract is so important in body fluid and electrolyte balance.*

A Triolo, MR Lappin: Acute medical diseases of the small intestine. In TR Tams (Ed.): *Handbook of small animal gastroenterology*. 2003, Saunders, St Louis, *Clinically useful information in an easy-to-read format.*

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* See the CD-ROM for a complete list of references

129 Chapter 129 Motility Disorders

Patricia M. Dowling, DVM, MSc, DACVIM, DACVCP

129.1 KEY POINTS

- Treatment of canine congenital and acquired megaesophagus is symptomatic, with protectants and histamine-2 blockers or serotonergic drugs used for esophageal reflux and esophagitis.
- Gastric emptying disorders can be treated with metoclopramide, serotonergic drugs, motilin receptor agonists, and acetylcholinesterase inhibitors.
- Intestinal transit disorders can be treated with serotonergic drugs, motilin receptor agonists, and acetylcholinesterase inhibitors.
- Feline megacolon can be treated with serotonergic drugs or acetylcholinesterase inhibitors.

129.2 INTRODUCTION

Gastrointestinal (GI) motility disorders are common and are challenging to diagnose and treat in both humans and animals. Therapy is directed toward correcting predisposing factors and utilizing prokinetic drugs to promote normal GI motility.

129.3 MEGAESOPHAGUS

Congenital megaesophagus is seen in a number of breeds of dogs, including Wirehaired Fox Terriers, Miniature Schnauzers, German Shepherds, Great Danes, Irish Setters, Labrador Retrievers, Newfoundlands, and Chinese Shar Peis. It is rare in cats, but Siamese cats may be predisposed. Congenital megaesophagus in dogs is due to organ-specific sensory dysfunction, whereby the distention-sensitive vagal afferent system innervating the esophagus is defective, but other contiguous and physiologically similar distention-sensitive vagal afferent systems are unaffected.[1] Acquired megaesophagus can develop in association with a number of primary diseases in dogs and cats, but most adult-onset cases are idiopathic.[2] Myasthenia gravis accounts for most cases with a known cause. Other causes of acquired megaesophagus include hypoadrenocorticism, lead poisoning, lupus erythematosus, and severe esophagitis. Inflammatory myopathies associated with megaesophagus in dogs include immune-mediated polymyositis, infectious and preneoplastic myositis, and dermatomyositis. Dogs with peripheral neuropathies, laryngeal paralysis, myasthenia gravis, esophagitis, and chronic or recurrent gastric dilation with or without volvulus are at an increased risk of developing megaesophagus. German Shepherds, Golden Retrievers, and Irish Setters are at increased risk for acquired megaesophagus.[2] Although often cited as a cause, a clear link between hypothyroidism and megaesophagus can not be demonstrated.

Regurgitation is the predominant symptom associated with megaesophagus, and a careful history can help distinguish between passive regurgitation and active vomition. The frequency of episodes and relation to time of feeding vary considerably. Puppies with congenital megaesophagus typically begin regurgitating when started on solid foods. Emaciation from malnutrition and aspiration pneumonia are the most common complications of megaesophagus.

Plain survey radiographs are often diagnostic, but contrast radiography may be useful to confirm the diagnosis and evaluate motility. Endoscopy also confirms the diagnosis and can identify esophagitis, which often occurs in dogs with megaesophagus. Routine hematology, serum biochemistries, and urinalysis should be performed to investigate primary disorders that can result in secondary megaesophagus. Additional diagnostic tests for acquired megaesophagus include serology for nicotinic acetylcholine receptor antibody and antinuclear antibody, adrenocorticotropic hormone stimulation, serum creatine phosphokinase activity, electromyography and nerve conduction velocity, and nerve and muscle biopsies.

Treatment of congenital megaesophagus is symptomatic, because traditional prokinetic drugs such as metoclopramide and cisapride have no effect on the striated muscle of the canine esophagus. Because the incidence of esophagitis is high, affected animals should be treated with sucralfate (1 g q8h for large dogs, 0.5 g q8h for smaller dogs, and 0.25 g q8-12h for cats) or a histamine-2 blocker (cimetidine 5 to 10 mg/kg PO q8-12h; ranitidine 1 to 2 mg/kg PO q12h; famotidine 0.5 to 1 mg/kg PO q12h). Animals with secondary megaesophagus should be treated for the primary disease. Myasthenia gravis in dogs is managed with pyridostigmine (1 to 3 mg/kg PO q12h), prednisone (1 to 2 mg/kg PO q12h), or azathioprine (2 mg/kg PO q24h initially). Affected animals should be fed small amounts of a high-calorie diet at frequent intervals from an elevated position to allow gravity to assist passage into the stomach. The Bailey Chair (http://www.geocities.com/bailey_chair/) is an example of a positioning device that may be helpful. If unable to maintain adequate nutritional intake in this manner, a temporary or permanent gastrostomy tube can be placed.

129.4 GASTRIC EMPTYING DISORDERS

Dog and cats frequently have gastric emptying disorders from mechanical obstruction or defective propulsion.[3] Defective propulsion is caused by abnormalities in myenteric neuronal or gastric smooth muscle function or antropyloroduodenal coordination. Primary problems associated with defective propulsion include infectious and inflammatory diseases, ulcers, and postsurgical gastroparesis. Delayed gastric emptying also occurs secondarily to electrolyte imbalances, metabolic derangements, drugs (cholinergic antagonists, adrenergic and opioid agonists), and peritonitis. In critically ill animals, delayed gastric emptying limits enteral nutrition, and the effects of severe disease further deplete caloric reserves, impairing wound healing, decreasing immune function, and increasing morbidity and mortality.[4]

The most common presenting complaint is chronic intermittent vomiting that occurs more than 8 hours after eating. Gastric distention may be discernible after eating and is relieved by vomiting. Additionally, some patients may have lost weight.

Although diagnosis and treatment of mechanical obstruction are straightforward, disorders of propulsion are more challenging. Other causes of chronic vomiting should be ruled out. Imaging studies are used to confirm delayed gastric emptying, the most common gastric motility disorder. Survey films, barium contrast studies, and fluoroscopy may all be used to document abnormal gastric emptying. Barium-impregnated polyspheres can be administered to measure the passage of various-sized beads. Endoscopy is used to rule out gastritis or obstructive disease. If no underlying cause is determined, a functional disorder of gastric emptying is diagnosed presumptively. Treatment consists of dietary modification and gastric prokinetic agents.[3] Animals should be fed frequent small meals that are low in fat and protein and high in carbohydrates (e.g., cottage cheese, rice, pasta).

129.5 SMALL INTESTINAL TRANSIT DISORDERS

Causes of small intestinal transit disorders include enteritis, postsurgical ileus, nematode impaction, intestinal sclerosis, and radiation enteritis.[5] Pseudoobstructions are functional obstructions caused by hypomotility and ileus; most are idiopathic. Intestinal stasis can result in bacterial overgrowth, and the absorption of endotoxin and bacteria can lead to endotoxemia and septicemia. Clinical signs depend on the location and cause of the disorder but typically include vomiting, diarrhea, and weight loss. Abdominal pain and distention may be noted.

With pseudoobstruction, survey radiographs show dilated bowel loops without evidence of a physical obstruction. Contrast studies or barium-impregnated polyspheres can demonstrate delayed transit through the small intestine. The hemogram findings are typically normal, but changes in the serum biochemical profile may be seen with protracted vomiting or diarrhea. Mechanical obstructions should be ruled out before treatment with prokinetic drugs. Additional therapy will be based upon the cause of the transit disorder and may include glucocorticoids and antimicrobial agents.

129.6 MEGACOLON

Idiopathic megacolon with constipation or obstipation is a common clinical condition in middle-aged cats.[6,7] Less common causes of constipation in cats are pelvic canal stenosis, dysautonomia, nerve injury, and Manx sacral spinal cord deformities. The underlying cause of megacolon in cats appears to be a generalized dysfunction of colonic smooth muscle.[8] Cats with megacolon typically suffer from reduced, absent, or painful defecation. The owner usually notices the cat making numerous unproductive attempts to eliminate in the litter box. When passed, feces are often dry and hard, and hematochezia may be present. Prolonged constipation may also cause anorexia, vomiting, and weight loss.

Colonic impaction is usually obvious on physical examination. Depending on the severity and duration of the condition, other clinical signs can include weight loss, abdominal pain, dehydration, and mesenteric lymphadenopathy. Results of complete blood counts and serum chemistries are typically normal, but metabolic causes of constipation, such as dehydration, hypokalemia, or hypocalcemia, can occasionally be detected. Abdominal radiography can document the extent of fecal impaction and identify exacerbating factors including foreign material (e.g., bones), intraabdominal masses, pelvic fractures, and spinal column abnormalities. Digital rectal examination should be performed very carefully but may be very helpful in identifying pelvic fractures, rectal diverticula, or neoplasia.

Therapy for constipation depends on the severity and the underlying cause. Mild to moderate cases typically are

managed with dietary modification, laxatives, and colonic prokinetic agents. Colectomy should be considered in cats whose disease is refractory to medical therapy. Cats have a generally favorable prognosis for recovery following colectomy, although mild to moderate diarrhea may persist for weeks to months postoperatively in some cases.

129.7 PROKINETIC DRUGS FOR GASTROINTESTINAL MOTILITY DISORDERS

129.7.1 Serotonergic Drugs

The enteric nervous system of the GI tract can function independently of the central nervous system (CNS) to control bowel function.[9] Because there are no nerve fibers that actually penetrate the intestinal epithelium, the enteric nervous system uses enteroendocrine cells such as the enterochromaffin cells as sensory transducers. Over 95% of the body's serotonin is located in the GI tract, and over 90% of that store is in the enterochromaffin cells that are scattered in the enteric epithelium from the stomach to the colon. The remaining serotonin is located in the enteric nervous system, where 5-HT acts as a neurotransmitter.

From the enterochromaffin cells, serotonin is secreted into the lamina propria in high concentrations and overflows into the portal circulation and intestinal lumen. The effect of serotonin on intestinal activity is coordinated by 5-HT receptor subtypes. The 5-HT_{1P} receptor initiates peristaltic and secretory reflexes, and so far no drug has been developed to target this particular receptor. The 5-HT_3 receptor activates extrinsic sensory nerves and is responsible for the sensation of nausea and induction of vomiting from visceral hypersensitivity. Therefore specific 5-HT_3 antagonists such as ondansetron and granisetron are used to manage the nausea and vomiting seen with chemotherapy.

Stimulation of the 5-HT_4 receptor increases the presynaptic release of acetylcholine and calcitonin gene–related peptide, thereby enhancing neurotransmission. This enhancement promotes propulsive peristaltic and secretory reflexes. Specific 5-HT_4 agonists such as cisapride or tegaserod enhance neurotransmission and depend on natural stimuli to evoke peristaltic and secretory reflexes. This makes these drugs very safe, because they do not induce perpetual or excessive motility. It is also the reason for the limitations of these drugs, because they will not be effective if enteric nerves have degenerated or become nonfunctional.

129.7.1.1 Cisapride

Cisapride was introduced in 1993 and was the most efficacious prokinetic drug in the management of human GI motility disorders. It also became popular for treating motility disorders in dogs and cats. Cisapride is chemically related to metoclopramide, but unlike metoclopramide, it does not cross the blood-brain barrier or have antidopaminergic effects. Therefore it does not have antiemetic action and it does not cause the extrapyramidal effects seen with metoclopramide. Cisapride is more potent and has broader prokinetic activity than metoclopramide, increasing the motility of the colon as well as that of the esophagus, stomach, and small intestine. Cisapride is useful in treating gastric stasis, idiopathic constipation, GI reflux, and postoperative ileus in dogs and cats. Cisapride is useful in treating cats with megacolon; in many cases it alleviates or delays the need for subtotal colectomy.[10]

Initially the only adverse side effects reported in humans were increased defecation, headache, abdominal pain and cramping, and flatulence, and cisapride appeared to be well tolerated by dogs and cats. As cisapride became widely used in the management of gastroesophageal reflux in humans, cases of heart rhythm disorders and deaths were reported. These cardiac problems in humans were highly associated with concurrent drug therapy or specific underlying conditions. Cisapride is metabolized by the liver by the cytochrome P-450 enzyme system. Cardiac abnormalities in humans were associated with concomitant administration of other drugs that inhibit cisapride's cytochrome P-450 system, thereby increasing cisapride blood concentrations.

Drugs known to inhibit the metabolism of cisapride include clarithromycin, erythromycin, troleandomycin, nefazodone, fluconazole, itraconazole, indinavir, and ritonavir. Because of the human cardiovascular side effects, the manufacturer of cisapride withdrew the product from sale in North America. Cisapride can be obtained only from compounding pharmacies in the United States and Canada and is formulated from active pharmaceutical ingredients. Because of the lack of standardized products, efficacy may vary, but a suggested dosage for cats is 2.5 to 5 mg PO q8-12h. Dosages of 0.5 to 1 mg/kg PO q8-12h are suggested for delayed gastric emptying in dogs. Cisapride is better absorbed when given with food, so it should be given 15 minutes before feeding.

129.7.1.2 Tegaserod

Tegaserod (Zelnorm) is a selective partial serotonin agonist approved for use in humans that is highly selective for the 5-HT_4 receptor and has weak agonist activity at the 5-HT_{1P} receptor.[11] As a partial agonist, tegaserod is less likely to induce receptor desensitization than are full agonists, so tolerance to therapy is unlikely to develop. Tegaserod stimulates gastric emptying in rats and dogs under normal or perturbed conditions. It accelerates colonic transit and normalizes intestinal transit after opioid-induced bowel dysfunction in dogs.[12,13] In the cat, tegaserod has an inhibitory effect on intramural mechanoreceptors in the rectum. This mechanism is believed to relieve the sensory symptoms of human patients with irritable bowel syndrome.[14]

Unlike cisapride, no clinically relevant pharmacokinetic and pharmacodynamic drug-drug interactions have been identified in humans or animals. The only significant side effect reported in human patients is transient diarrhea. A dose of 0.05 to 1 mg/kg PO or IV q12h is suggested pending further studies in dogs and cats.

129.7.2 Metoclopramide

Metoclopramide (Reglan) is a central dopaminergic antagonist and peripheral 5-HT_3 receptor antagonist and 5-HT_4 receptor agonist with GI and CNS effects. Metoclopramide stimulates and coordinates esophageal, gastric, pyloric, and duodenal motor activity. It increases lower esophageal sphincter tone and stimulates gastric contractions, while relaxing the pylorus and duodenum. Metoclopramide is indicated for nausea and vomiting associated with chemotherapy and as an antiemetic for dogs with parvoviral enteritis. In clinically normal dogs, metoclopramide does not increase gastric emptying and in dogs with gastric dilation and volvulus, metoclopramide does not change gastric myoelectric and motor activities in a way that would promote increased gastric emptying.[15-17] Metoclopramide has little or no effect on colonic motility.

Metoclopramide readily crosses the blood-brain barrier, where dopamine antagonism at the chemoreceptor trigger zone produces an antiemetic effect. However, dopamine antagonism in the striatum causes adverse effects known collectively as extrapyramidal symptoms, which include involuntary muscle spasms, motor restlessness, and inappropriate aggression. Many practitioners can relate stories of frenzied dogs and cats and resulting human injuries after metoclopramide administration. If recognized in time, the extrapyramidal signs can be reversed by restoring an appropriate dopamine-to-acetylcholine balance with the anticholinergic action of diphenhydramine hydrochloride (1 mg/kg IV).

Metoclopramide is given at 0.2 to 0.5 mg/kg PO or SC q8h, at least 30 minutes before a meal and at bedtime. It can also be given by continuous intravenous infusion at 0.01 to 0.02 mg/kg/hr.

129.7.3 Motilin Receptor Agonists

Macrolide antibiotics, including erythromycin and clarithromycin, are motilin receptor agonists. At microbially ineffective dosages, they stimulate migrating motility complexes and antegrade peristalsis in the proximal GI tract. They also appear to stimulate cholinergic and noncholinergic neuronal pathways that increase motility. Erythromycin increases gastroesophageal sphincter pressure in dogs and cats, so it should be useful in treating gastroesophageal reflux and reflux esophagitis.[12] Erythromycin increases the gastric emptying rate in normal dogs; however, large food chunks may enter the small intestine and be inadequately digested.[3] Erythromycin accelerates colonic transit in the dog and stimulates canine, but not feline, colonic smooth muscle in vitro.[12]

Human pharmacokinetic studies indicate that erythromycin suspension is the ideal form for administration of erythromycin as a prokinetic agent. The suggested prokinetic dosage is 0.5 to 1 mg/kg PO q8h. Other macrolide antibiotics have prokinetic activity with fewer side effects than erythromycin and may be suitable for use in small animals. Nonantibiotic derivatives of erythromycin are being developed as prokinetic agents.

129.7.4 Acetylcholinesterase Inhibitors

Ranitidine and nizatidine are two histamine-2 receptor antagonists that are prokinetic agents in addition to inhibiting gastric acid secretion in dogs and rats. Their prokinetic activity is due to acetylcholinesterase inhibition, with the greatest activity seen in the proximal GI tract. Cimetidine and famotidine are not acetylcholinesterase inhibitors and do not have prokinetic effects. Ranitidine and nizatidine stimulate GI motility by increasing the amount of acetylcholinesterase available to bind smooth muscle muscarinic cholinergic receptors. They also stimulate feline colonic smooth muscle contraction through a cholinergic mechanism.

Ranitidine given at 1 to 2 mg/kg PO q12h inhibits gastric acid secretion and stimulates gastric emptying. Nizatidine, at gastric antisecretory dosages of 2.5 to 5 mg/kg PO q12h, also has prokinetic effects. Ranitidine causes less interference with cytochrome P-450 metabolism of other drugs than cimetidine, and nizatidine does not affect hepatic microsomal enzyme activity, so both drugs have a wide margin of safety.

129.8 SUGGESTED FURTHER READING*

RW Bertoy: Megacolon in the cat. *Vet Clin North Am Small Anim Pract*. **32**, 2002, 901, *Review of the current approaches to feline megacolon*.

AR Gaynor, FS Shofer, RJ Washabau: Risk factors for acquired megaesophagus in dogs. *J Am Vet Med Assoc*. **211**, 1997, 1406, *Case-control study that identified the risk factors for acquired megaesophagus to be evaluated for peripheral neuropathies, laryngeal paralysis, acquired myasthenia gravis, esophagitis, and chronic or recurrent gastric dilation*.

JA Hall, RJ Washabau: Diagnosis and treatment of gastric motility disorders. *Vet Clin North Am Small Anim Pract*. **29**, 1999, 377, *Review of the diagnosis and treatment of gastric motility disorders*.

* See the CD-ROM for a complete list of references

130 Chapter 130 Gastrointestinal Hemorrhage

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130.1 KEY POINTS

- Gastrointestinal (GI) hemorrhage is an important cause of blood loss anemia.
- In dogs and cats GI ulceration is the most commonly reported cause of GI hemorrhage.
- Nonsteroidal antiinflammatory drugs and hepatic disease are frequent causes of GI ulceration in dogs.
- Neoplasia is a common cause of GI ulceration in cats.
- Severe thrombocytopenia should not be overlooked as a cause of GI hemorrhage in dogs.
- Hematemesis and melena suggest GI hemorrhage but are not always noted.
- With acute severe GI hemorrhage, the primary objective is to rapidly assess the patient's cardiovascular status and institute aggressive resuscitative efforts if shock is present.
- It is reasonable to administer GI protectants before confirming the cause of GI hemorrhage.
- Most cases of GI hemorrhage respond well to medical treatment, although surgery may be indicated in others.

130.2 INTRODUCTION

Gastrointestinal (GI) hemorrhage is an important cause of blood loss anemia and a potentially life-threatening condition in dogs.[1] It is reported less frequently in cats. It may be acute or chronic, occult (no visible blood) or overt (grossly visible blood), and can vary from mild, self-limiting states to severe life-threatening conditions. Significant GI hemorrhage can often be detected during history and physical examination. However, on occasion even acute severe GI hemorrhage may be overlooked if signs localizing blood loss to the GI tract are not present or if concurrent disease obscures the diagnosis.[2,3] In addition, because even mild cases may progress to life-threatening events, it is important to rapidly identify patients with GI hemorrhage and institute therapies to prevent their deterioration.

130.3 ETIOLOGY

GI hemorrhage in dogs and cats can be the result of a primary insult to the GI tract or may be secondary to a systemic disease process. It may originate in the esophagus, stomach, small intestine, or large intestine. As such, a number of pathologic processes have been associated with GI hemorrhage. In general, these can be divided into three broad categories: diseases causing ulcers, diseases causing coagulopathies, and diseases associated with vascular anomalies. Animals may have single or multiple predisposing causes.[1,4]

The most commonly reported cause of GI hemorrhage in dogs and cats is GI ulceration.[3-6] The severity of GI hemorrhage associated with ulcers varies with the degree and extent of mucosal erosion. With erosion into an underlying artery, the magnitude of bleeding is related to the size of the arterial defect and the diameter of the artery.[7] Diseases associated with GI ulceration in dogs and cats are listed in Box 130-1. Nonsteroidal antiinflammatory drugs (NSAIDs) and hepatic disease are the most commonly reported risk factors for ulcers in dogs (Color Plate 130-1).[4] Neoplasia is a common risk factor for ulcers in cats, with systemic mastocytosis, gastrinoma, intestinal lymphosarcoma, and adenocarcinoma being the most commonly reported tumors.[3] Inflammatory bowel disease may also be an important nonneoplastic cause of GI ulceration in cats and dogs.[3] Stress ulcers are a frequent cause of GI hemorrhage in critically ill human patients and have been reported in dogs and cats following hypovolemia and surgery.[3,8] The true incidence and significance of stress ulcers in critically ill cats and dogs has not been determined, but should be considered in patients that develop GI hemorrhage while in the hospital.

Coagulation disorders associated with GI hemorrhage include rodenticide toxicity, disseminated intravascular coagulation, coagulation factor deficiencies (factor XII and prekallikrein deficiency), and thrombocytopenia.[1,5] Thrombocytopenia is the most common coagulation disorder resulting in GI hemorrhage in dogs and should not be overlooked.[1] Coagulation disorders resulting in GI hemorrhage appear to be less common in cats.

Vascular anomalies, because of the high incidence of varices, are a common cause of GI hemorrhage in humans. In contrast, only a few cases of vascular anomaly have been reported in the veterinary literature and it appears to be an infrequent cause of GI hemorrhage in dogs and cats.[9] It should be considered when more common causes of GI hemorrhage have been ruled out.

130.4 HISTORY AND PHYSICAL EXAMINATION

With extensive hemorrhage, vomiting, diarrhea, or ulcer perforation, patients with GI hemorrhage may present in a state of shock due to blood loss, hypovolemia, endotoxemia, or sepsis. Examination findings consistent with shock include tachycardia, diminished or thready arterial pulses (particularly peripheral), cool extremities, prolonged capillary refill time, and pale mucous membranes. Aggressive resuscitative therapies to reverse the state of shock take precedence (see Chapters 10 and 65, Shock and Shock Fluids and Fluid Challenge, respectively), and localization of the site of hemorrhage and tailored therapies may need to be delayed until the cardiovascular system is stable.

Once resuscitative efforts have commenced, a complete history and physical examination should be performed. 566 Hematemesis (vomitus with the appearance of coffee grounds or frank blood), hematochezia (passage of bright red 567 or frank blood with or without stool), or melena (black tarry stool) suggests the GI tract as a source of hemorrhage. However, these signs are not always evident clinically and may not appear until significant GI hemorrhage has occurred.[3,4,10] With duodenal hemorrhage, if reflux of duodenal contents into the stomach is insufficient, blood may not be visible in the vomitus.[11] However, when it is present, hematemesis suggests ongoing blood loss.[12] Diseases of the nasal cavity and oropharynx occasionally can cause hematemesis and melena from swallowing blood of epistaxis or hemoptysis (coughing of blood), and these causes should be considered. In addition, activated charcoal, bismuth (Pepto-Bismol), and diets high in iron can result in dark stools and should not be confused with melena.[13]

A history of aspirin or other NSAID administration is not uncommon.[4,10,14] There are case reports of GI ulceration, hemorrhage, and GI perforation occurring in veterinary patients that have received selective cyclooxygenase inhibitors at recommended therapeutic dosages.[10] Decrease or loss of appetite with or without other signs of GI disease should prompt consideration of GI side effects in any patients receiving NSAIDs. The medication should be discontinued and the patient should be examined. In cases of thrombocytopenia or coagulation disorders, there may be a history of bleeding from other sites of the body including the nasal cavities or urinary tract. Thorough examination of the mucosal surfaces may reveal petechiae in severely thrombocytopenic patients. A search for subcutaneous nodules or masses may detect underlying mast cell tumors.

Because GI hemorrhage may be insidious in onset, especially when chronic, the abdomen should be examined carefully. Abdominal palpation may localize areas of pain (tenderness, voluntary or involuntary guarding) or induce nausea, identify masses or foreign objects, or detect abdominal distention or a fluid wave. Splenomegaly or hepatomegaly may be identified in patients with mastocytosis, other neoplasia, or hepatic diseases. During initial evaluation or resuscitation of the patient, a careful rectal examination should be performed to detect frank blood or melena and to look for masses or foreign bodies.

Although hemorrhage from any site in the GI tract can be serious, upper GI hemorrhage tends to be more severe.[12,13] In addition, the etiology as well as the diagnostic tests and therapies for upper and lower GI hemorrhage may vary, making localization of the site of hemorrhage important.[5,13] Hematemesis or melena suggests upper GI hemorrhage.[13] However, it is important to remember that it is the amount of time the blood remains in the GI tract and not necessarily the site of bleeding that determines its color.[13,14] Delayed GI transit time and retention of blood in the colon could result in melena associated with a lower GI tract lesion.[13,15] Hematochezia is usually reflective of large intestinal, rectal, or anal hemorrhage; however, severe acute intestinal hemorrhage can act as a cathartic, significantly decreasing GI transit time.[12-14] This may result in the passage of frank blood in the stool following significant blood loss into the upper GI tract.[12,14]

130.5 DIAGNOSTIC TESTS

GI hemorrhage is confirmed when a source of bleeding is localized to the GI tract. Patients with signs of shock should have emergency minimum blood tests performed (hematocrit, total solids, blood urea nitrogen [BUN], glucose and, if available, pH, lactate, and electrolytes) while resus-citative efforts and a search for the underlying cause are undertaken. In cases suspected to have hemoabdomen or septic peritonitis, abdominocentesis, emergency abdominal sonography, and diagnostic peritoneal lavage are warranted and may be performed during initial resuscitation of the patient. Once resuscitative efforts have commenced or the patient's condition has stabilized, other diagnostic modalities should be considered.

130.5.1 Box 130-1 Diseases Associated With GI Ulceration and Hemorrhage in Dogs and Cats

130.5.1.1 Drug Administration

NSAIDs

Glucocorticoids

130.5.1.2 Systemic and Metabolic Diseases

Hepatic disease

Uremia

Pancreatitis

Hypoadrenocorticism

130.5.1.3 Ischemic Events

GDV

Mesenteric volvulus

Mesenteric thrombosis

Intussusception

130.5.1.4 Neurologic Disease

Head trauma

IVDD

Mucosal trauma

Foreign bodies

130.5.1.5 Fungal Infections

Pythium

Histoplasma

130.5.1.6 Bacterial Infections

Salmonella

Clostridium spp

Campylobacter

Helicobacter (controversial)

130.5.1.7 Parasitic Infections

Hookworms

Whipworms

Coccidia

Roundworms

130.5.1.8 Viral Infections

Parvovirus

Coronavirus

130.5.1.9 Algal Infections

Protothecosis

Systemic neoplasia

Mastocytosis

Gastrinoma

130.5.1.10 Gastrointestinal Neoplasia

Lymphoma

Adenocarcinoma

Leiomyoma

Leiomyosarcoma

130.5.1.11 Stress of Critical Illness

Major surgery

Hypovolemia

Sepsis

130.5.1.12 Miscellaneous

IBD

Polyps

HGE

GDV, Gastric dilatation-volvulus; *GI,* gastrointestinal; *HGE,* hemorrhagic gastroenteritis; *IBD,* inflammatory bowel disease; *IVDD,* intervertebral disk disease; *NSAIDs,* nonsteroidal antiinflammatory drugs.

130.5.2 Tests to Help Detect Presence of Gastrointestinal Hemorrhage

When GI hemorrhage is not obvious on history or physical examination findings, certain hematologic and biochemical abnormalities may suggest its presence. Anemia of undetermined origin should prompt consideration of GI hemorrhage. The finding of microcytic, hypochromic anemia (iron deficiency anemia) is reported following chronic blood loss into the GI tract.[4] However, because iron deficiency anemia takes time to develop, normocytic normochromic anemia is more common in cases of recent GI hemorrhage.[1,4] A high BUN-to-creatinine ratio (>20) has been reported with GI hemorrhage, especially when it occurs in the upper GI tract.[15] This phenomenon has been explained by volume depletion and intestinal absorption of proteins, including digested blood, into the circulatory system.[15] Large bowel hemorrhage is reported to have little effect on BUN levels.[15,16] However, as diseases resulting in increased protein metabolism (fever, burns, infections, starvation, and administration of glucocorticoids) may also result in an increased BUN-to-creatinine ratio, they should be considered before concluding that GI hemorrhage is the cause.[1,15] It should also be noted that many dogs with GI hemorrhage do not have an elevation in the BUN concentration.[1]

In equivocal cases of GI hemorrhage a fecal occult blood test, most of which rely on the peroxidase activity of hemoglobin, may be performed. Although it may be helpful for detecting occult GI hemorrhage, diets containing red meat or having high peroxidase activity, such as fish, fruits, or vegetables, can cause false-positive results.[17] The presence of peroxidase-producing bacteria within the GI tract may also cause false-positive results.[17] These factors must be considered when interpreting positive chemical-based fecal occult blood test results.

It has been recommended that animals be fed a meat-free diet for at least 72 hours before a fecal occult blood test.[18] On the other hand, a negative fecal occult blood test result does rule out significant GI hemorrhage.[2] When significant gastric hemorrhage is suspected but not confirmed, passage of a nasogastric tube and aspiration of the stomach contents may confirm and help localize the site of GI hemorrhage, although the procedure may cause discomfort and false-negative results have been reported.[11,16]

130.5.3 Tests to Help Identify Underlying Causes

Once GI hemorrhage is confirmed or suspected, a search for an underlying cause should be pursued. This often includes a coagulation profile, complete blood count, routine bio-chemistry profile, electrolytes, adrenocorticotropic hormone stimulation testing, imaging, and endoscopy as indicated.

The coagulation profile may identify coagulopathies such as rodenticide intoxication or clotting factor deficiencies. It may also detect prolonged bleeding times that are not the direct cause of GI hemorrhage but that significantly exacerbate blood loss. The platelet count is important, because immune-mediated thrombocytopenia is a common cause of moderate to severe GI hemorrhage in dogs.[1] An elevated hematocrit in a patient with acute hemorrhagic diarrhea and a relatively normal plasma protein concentration is suggestive of hemorrhagic gastroenteritis.[18]

Given that hepatic and renal disease are reported causes of GI ulceration and hemorrhage, particular attention should be paid to the biochemical markers reflective of these diseases (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and bilirubin in cases of hepatic disease; and urea, creatinine, and phosphorus in cases of renal disease). Because hypoadrenocorticism has been reported as a cause of severe GI hemorrhage in the dog, electrolyte levels should be evaluated and an adrenocorticotropic hormone (ACTH) stimulation test performed if another cause for GI hemorrhage cannot be found.[19] Fecal smears, cultures, and parvovirus testing may be indicated if infectious disease is suspected. Measurement of gastrin levels is recommended in cases of recurrent GI ulceration and in cases that fail to respond to medical therapy.[4]

Radiographs may detect foreign bodies, masses, or free air in the peritoneal cavity. Pneumoperitoneum is suggestive of GI perforation in a patient that has not undergone recent abdominal surgery. Although contrast radiographs may identify mucosal defects as a cause of GI hemorrhage, they generally have been replaced by ultrasonography and endoscopy.[4,16] Ultrasonography often will identify foreign bodies and masses, and may help to identify concurrent GI perforation when present.[20,21] The use of ultrasonography to identify ulcers in dogs has been described. It allows evaluation of the intestinal wall structure and thickness and can detect the presence of a defect or crater.[21] When used serially, it may help determine changes in response to therapy and has suggested the need for surgery in some instances.[21] Ultrasonography has also been reported in the assessment of cats with GI ulceration.[3]

Endoscopy is considered the most sensitive test to evaluate upper GI tract hemorrhage and ulcers, although patients must be optimally resuscitated before the procedure.[7,16] It often provides a diagnosis, helps assess prognosis, and may have therapeutic benefits (i.e., foreign body retrieval). In addition to allowing direct visualization of the mucosa, it permits biopsies for histology and culture, which may be required to identify lesions and infectious diseases (i.e., neoplasia, inflammatory bowel disease, protothecosis). The disadvantages of endoscopy include the need for anesthesia, its limitation to the proximal GI tract and colon, the potential to exacerbate GI hemorrhage, and the possibility of causing iatrogenic ulcer perforation.[14]

If the above diagnostic procedures fail to identify the cause of significant ongoing GI hemorrhage, abdominal exploratory surgery, scintigraphy using technetium-labeled red blood cells, and arteriography should be considered.[2,16,18] Scintigraphy has been demonstrated to aid in localization of GI hemorrhage in dogs, and arteriography may help identity GI vascular anomalies.[2,9,18]

130.6 TREATMENT

The treatment priority in patients with GI hemorrhage is to stabilize the cardiovascular system, control ongoing hemorrhage, treat existing ulcers, prevent bacterial translocation, and to identify and address the underlying cause. The initial priority is to rapidly identify and reverse any signs of shock (see Chapters 10 and 65, Shock and Shock Fluids and Fluid Challenge, respectively).

Depending on the duration and extent of blood loss, administration of packed red blood cells, whole blood, or oxyglobin may be indicated. In the patient with severe acute GI hemorrhage, this is often implemented as part of the initial resuscitation protocol. In patients that do not display initial signs of shock, determining when a blood transfusion should be given is less clearly defined. The decision to transfuse all patients at a specified hematocrit remains controversial. The hematocrit at which a patient requires a transfusion will vary depending on the degree and rate of blood loss, hemodynamic status, initial and subsequent hematocrits, presence of concurrent illness, and severity of clinical signs.[22] If the patient displays clinical signs attributable to a decrease in oxygen delivery (i.e., tachycardia, hyperlactatemia, tachypnea) or if serial measurements reveal a decreasing hematocrit after initiating therapy, a blood transfusion is indicated.[22]

If GI hemorrhage is the result of a primary coagulopathy or is exacerbated by a secondary coagulopathy (i.e., disseminated intravascular coagulation, hepatic failure, shock, or dilution with aggressive fluid therapy), fresh frozen plasma should be considered. In patients with persistent GI hemorrhage as a result of thrombocytopenia, vincristine may increase the release of platelets from the bone marrow, although the function of these platelets has been questioned.[23]

Iced saline gastric lavage has been suggested as a therapy to decrease GI hemorrhage[5,6]; however, the current consensus in the human literature is that it be avoided. Iced saline gastric lavage has not been proven to slow hemorrhage, is known to cause discomfort, and can rapidly lower core body temperature, which was demonstrated to prolong bleeding in an experimental canine study.[6,14]

Animals with hematemesis and melena should be treated for GI ulcers until proven otherwise. Medications known to cause ulcers should be discontinued (i.e., NSAIDS). Given the association between GI hemorrhage and steroids in dogs, unless they are considered essential to therapy (i.e., hypoadrenocorticism, immune-mediated diseases), they should also be discontinued.

It is reasonable to administer GI protectants before confirming the cause of GI hemorrhage, given that ulcers are the most common cause of GI hemorrhage in dogs and cats, and GI protectants have a wide safety margin. In addition, intraluminal gastric acid neutralization may slow GI hemorrhage by promoting mucosal homeostasis.[7,24] Commonly used GI protectants include acid suppressants such as histamine-2 receptor antagonists (cimetidine, ranitidine, famotidine) and proton pump inhibitors (omeprazole, pantoprazole), mucosal binding agents such as sucralfate, and synthetic prostaglandins such as misoprostol. There are no veterinary studies to conclude which gastroprotectants or combination of gastroprotectants are most efficacious in the management of GI ulcers. However, a study demonstrated that famotidine (0.5 mg/kg IV q12h), omeprazole (1 mg/kg PO q24h), and pantoprazole (1 mg/kg IV q24h) significantly suppressed gastric acid secretion in dogs, but ranitidine (2 mg/kg IV q24h) failed to show significant gastric acid suppression at the dosage evaluated.[24]

Although histamine-2 antagonists, proton pump inhibitors, sucralfate, and misoprostol have been administered concurrently, most cases of suspected GI ulceration are managed with either a histamine-2 antagonist or proton pump inhibitor and sucralfate.[4,14] In cases of NSAID toxicity, misoprostol may provide additional benefit. In deciding which medications to use, consideration should be given to the route of drug administration because absorption of medications administered orally in critically ill patients has been questioned, and many dogs with GI hemorrhage are vomiting, which may further limit the utility of oral medications. In patients that have persistent vomiting, antiemetics can be used. Metoclopramide, given as a constant intravenous infusion (1 to 2 mg/kg q24h), is often tried initially. Cases refractory to metoclopramide may benefit from additional antiemetics such as odansetron. Because many causes of GI hemorrhage are associated with discomfort and pain, analgesics such as an opioid should be considered.

In cases with significant GI hemorrhage, broad-spectrum antibiotics (i.e., a penicillin and an aminoglycoside or fluoroquinolone, or a combination of a cephalosporin, metronidazole, and an aminoglycoside or fluoroquinolone) are warranted because of the risk of GI mucosal barrier compromise and bacterial translocation. Ideally, samples for culture and sensitivity (i.e., urine and blood) should be collected before starting antibiotic therapy.

Most cases of GI hemorrhage can be managed medically. In cases of severe GI ulceration and hemorrhage refractory to medical treatment, endoscopic hemostasis may be beneficial. Ulcer hemostasis has been described by injecting epinephrine or 98% alcohol through an endoscope sclerotomy needle into the base of an ulcer.[7,25] The minimally invasive use of Endoclips or endoscopic thermal, electric, and laser cautery has been described to control GI hemorrhage secondary to vascular anomalies and ulcers in humans and may be applicable to veterinary medicine.[7,11] Surgery can be avoided in most cases, but is indicated for preexisting surgical disease (foreign body, tumor, septic abdomen) in patients at risk of exsanguination or perforation (based on endoscopy or serial sonographic evaluation), or if the patient fails to respond to medical therapy.

Because of the large number of disease conditions that can result in GI hemorrhage, therapy directed toward correcting the underlying cause is variable (i.e., surgery for foreign bodies or tumors, steroids for hypoadrenocorticism, immunosuppressives for immune-mediated thrombocytopenia, discontinuation of NSAIDs). In considering the underlying cause, it is important to consider related or unrelated coagulation abnormalities (i.e., liver disease causing ulceration and a clotting factor deficiency) and to address concurrent diseases that may exacerbate GI hemorrhage (i.e., uremia in a patient on NSAIDs).

130.7 PROGNOSIS

Many cases of GI hemorrhage are self-limiting and the prognosis varies with the underlying cause. In cases of moderate to severe GI hemorrhage requiring a blood transfusion, the prognosis is reportedly fair to poor, with a mortality rate of 29% to 45%.[1]

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130.8 SUGGESTED FURTHER READING*

JM Liptak, GB Hunt, VRD Barrs, et al.: Gastroduodenal ulceration in cats: Eight cases and a review of the literature. *J Feline Med Surg*. **4**, 2002, 27–42, *A small study with a good review of the literature concerning GI ulcers in cats*.

ME Stanton, BM Ronald: Gastroduodenal ulceration in dogs: retrospective study of 43 cases and literature review. *J Vet Intern Med*. **3**, 1989, 238, *A nice retrospective study and review of GI ulceration in dogs, including the pathophysiology of ulcer development in dogs with various underlying diseases*.

JE Waldrop, EA Rozanski, LM Freeman, et al.: Packed red blood cell transfusions in dogs with gastrointestinal hemorrhage: 55 cases (1999-2001). *J Am Anim Hosp Assoc*. **39**, 2003, 523, *One of the few publications investigating causes of GI hemorrhage in veterinary patients and an excellent paper addressing causes and management of patients with severe acute GI hemorrhage*.

RJ Washabau: Acute gastrointestinal hemorrhage. Part I. Approach to patients. *Comp Cont Educ Pract Vet*. **1**, 1996, 1317, *In conjunction with reference that follows, one of the most complete reviews of acute GI hemorrhage published in the veterinary literature*.

RJ Washabau: Acute gastrointestinal hemorrhage. Part II. Causes and therapy. *Comp Cont Educ Pract Vet*. **1**, 1996, 1327, *In conjunction with preceding reference, one of the most complete reviews of acute GI hemorrhage published in the veterinary literature*.

* See the CD-ROM for a complete list of references

131 Chapter 131 Vomiting and Regurgitation

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131.1 KEY POINTS

- It is important to differentiate between vomiting and regurgitation before proceeding with further diagnostic testing or therapy.
- Idiopathic megaesophagus is the most common cause of persistent regurgitation in the adult dog. Myasthenia gravis is the most common cause of secondary megaesophagus, accounting for 20% to 30% of all cases.
- Aspiration pneumonia is the most important cause of morbidity in the regurgitating patient.
- The multitude of differential diagnoses for vomiting can be subdivided into primary gastrointestinal and other causes.
- Abdominal radiographs should be obtained in all patients with acute vomiting. Abdominal ultrasonography may be a more useful imaging modality in patients with chronic vomiting.

131.2 DIFFERENTIATION OF VOMITING AND REGURGITATION

Before formulating a diagnostic and therapeutic plan, it is important to define the patient's clinical problem. Most importantly, vomiting and regurgitation must be distinguished; pet owners may not differentiate between the two problems, but the diagnostic investigations and treatment options will differ significantly. Occasionally pet owners will describe the harsh coughing and retching of canine infectious tracheobronchitis as vomiting. In most cases the problem can be defined accurately after taking a thorough history. Historic findings likely to assist in the differentiation between vomiting and regurgitation are presented in Table 131-1. Premonitory signs, active abdominal contractions, and bile are the characteristics that are most useful for making a diagnosis in vomiting animals and that are uncommonly seen in regurgitating patients. However, regurgitating animals may stretch and arch their necks, mimicking abdominal contractions, and the response to pain from an inflamed or ulcerated esophagus may resemble the classic signs of nausea.

It is important to distinguish true bile from the froth and saliva that animals with esophageal disease may regurgitate. Although relatively nonspecific, a further factor that may assist in the definition of the problem is the frequency of the episodes. Animals with esophageal disease may regurgitate saliva as frequently as hourly, yet remain bright and systemically healthy. A vomiting animal is unlikely to sustain this frequency of vomiting without becoming unwell.

131.3 REGURGITATION

131.3.1 Definition

Regurgitation is the passive ejection of food, water, or saliva associated with esophageal or, less commonly, pharyngeal disease.

131.3.2 Clinical Consequences of Regurgitation

The most significant clinical complication of regurgitation is aspiration pneumonia. Any patient with persistent regurgitation is at risk of aspiration pneumonia, and measures to reduce its occurrence should be instigated. Aspiration pneumonia is the most likely indication for hospitalization and intensive treatment of regurgitating patients. In the absence of aspiration pneumonia or other disease, most patients are able to maintain good hydration, although persistent regurgitation of undigested food may lead to marked weight loss.

Table 131-1 Comparison of the Key Features of Vomiting and Regurgitation

Vomiting	Regurgitation
Premonitory symptoms (nausea) often seen (hypersalivation, depression, discomfort)	No premonitory symptoms
Active abdominal contractions	Passive ejection of food
May occur at any time	Typically occurs shortly after ingestion of food
Digested food	Undigested food, may conform to the cylindric shape of the esophagus
Bile may be present	No bile

131.3.3 Differential Diagnoses

Regurgitation is associated with esophageal or pharyngeal disease. It is more common in dogs than in cats. In most cases the problem is localized to the esophagus or pharynx, but it is sometimes a manifestation of systemic disease. Common differential diagnoses are provided in Box 131-1. Idiopathic megaesophagus is the most common cause of regurgitation in the adult dog, and most middle-aged to older patients with uncomplicated regurgitation prove to have this disease.[1] However, it should be noted that focal myasthenia gravis is a significant cause of megaesophagus in the absence of other neurologic signs.

Many other concurrent diseases have been reported as causes of megaesophagus but epidemiologic evidence of an association is lacking.[2] It is reasonable to exclude these diseases from the differential diagnosis if other clinical and clinicopathologic changes are lacking and the problem list is limited to regurgitation.

131.3.4 Diagnostic Approach

131.3.4.1 History

Important historic information includes access to drugs or caustic substances and recent drug therapy or anesthesia that may have precipitated esophagitis. Most cases of drug-induced esophagitis are as a result of doxycycline administration, but many drugs have the potential to cause this side effect. Animals with esophagitis may also show signs of apparent esophageal discomfort, such as pain on swallowing (odynophagia), repeated swallowing attempts, lip smacking, and arching of the neck. These signs are seen less often in patients with megaesophagus, most of which regurgitate without premonitory signs and show no odynophagia.

Most animals that do not have odynophagia maintain a good appetite and will often attempt to eat the regurgitated ingesta. Other systemic signs such as lethargy, anorexia, vomiting, and diarrhea are not seen with uncomplicated esophageal disease and suggest a concurrent disease process or an underlying cause for the esophageal disease. Coughing or a sudden deterioration in the patient's clinical status should alert the clinician to the possibility of aspiration pneumonia.

131.3.4.2

Physical Examination

The physical examination should include a thorough oral examination and palpation of the neck. Abnormalities in the neck may include masses, palpable esophageal dilation, or pain. In some cases, palpation of the esophagus may elicit regurgitation or discomfort. Any crackles in the lung fields should be noted, but these should be differentiated from sounds of fluid in the esophagus.

131.3.4.2.1

Box 131-1 Important Differential Diagnoses for Regurgitation

131.3.4.2.1.1

Pharyngeal Disease

Cricopharyngeal achalasia

Focal or generalized neuromuscular disease

Foreign body

Neoplasia

131.3.4.2.1.2

Esophageal Disease

Hypomotility: megaesophagus

Congenital

Idiopathic (primary)

Secondary

- Myasthenia gravis (20% to 30% of cases)
- Generalized neuromuscular disease
- Hypoadrenocorticism
- Lead toxicity

- Hypothyroidism

Inflammation: esophagitis

Drug: chemical-induced

Gastroesophageal reflux

- General anesthesia
- Hiatal hernia
- Idiopathic

Lupus myositis

Spirocerca lupi infection

Mechanical obstruction

Esophageal stricture

Foreign body

Neoplasia

Vascular ring anomalies

Extraluminal compression (e.g., mediastinal mass)

Hiatal hernia

Gastroesophageal intussusception

131.3.4.3

Clinical Pathology

Routine hematology and biochemistry may show evidence of an underlying cause of megaesophagus. Results are unremarkable in most patients with uncomplicated idiopathic megaesophagus.

131.3.4.4 Diagnostic Imaging

Thoracic radiography is the most important and useful imaging modality for evaluating patients with regurgitation. Plain radiographs will be diagnostic in most cases of megaesophagus and foreign body obstruction. Plain radiographs may also show evidence of secondary aspiration pneumonia or mediastinal masses. Two lateral radiographs and an orthogonal view should be obtained to evaluate all lung fields. If plain radiographs do not show any abnormalities, contrast studies or endoscopy may be indicated. Abdominal ultrasonography rarely provides useful information in animals with regurgitation.

131.3.4.5 Further Diagnostic Testing

Serum should be submitted for acetylcholine receptor antibody assay on all patients with megaesophagus. Additional tests to consider based on clinical suspicion include an adrenocorticotropic hormone stimulation test, serology for antinuclear antibody, serum creatine phosphokinase activity, electromyography and nerve conduction velocity, and muscle and nerve biopsy. Evidence for an association with hypothyroidism is lacking, but thyroid function (thyroid stimulating hormone assay, thyroid stimulating hormone stimulation, free and total thyroid hormone levels) testing may be warranted in individual patients with other suspicious signs.[2] Most patients with megaesophagus secondary to hypoadrenocorticism will have electrolyte changes and other systemic signs.

131.3.5 General Treatment Guidelines

Most animals with regurgitation are stable and well hydrated and do not require therapy before a definitive diagnosis is made. In the absence of concurrent disease, these patients can be treated on an outpatient basis and do not require hospitalization. Empiric treatment with a histamine-2 receptor antagonist, prostaglandin analog, or proton pump inhibitor, with or without the addition of sucralfate, may be warranted (see Chapter 181, Gastrointestinal Protectants). Bethanechol stimulates esophageal contractions in some affected dogs and may be a useful prokinetic agent in those with megaesophagus. Smooth muscle prokinetic agents such as metoclopramide and cisapride are not effective on the striated muscle of the canine esophageal body.

Animals with secondary aspiration pneumonia require more intensive therapy and monitoring. These patients should be started on broad-spectrum antibiotics (see Chapter 23, Aspiration Pneumonitis and Pneumonia) and may require supplemental oxygen (see Chapter 19, Oxygen Therapy). Prolonged or repeated courses of antibiotics may be required and, when possible, airway samples should be collected for cytology and culture before initiating antibiotic therapy. If regurgitating animals require hospitalization, the priority should be to prevent aspiration pneumonia by feeding a high-calorie diet in small frequent meals from an elevated or upright position, and dietary consistency should be tailored to the animal. Although intuitively a firm diet would appear to reduce the risk of aspiration, many patients will have less frequent regurgitation when fed a more liquid ration. Animals that cannot maintain adequate nutritional balance with oral intake should be fed using a temporary or permanent gastrostomy tube (see Chapter 13, Enteral Nutrition).

131.3.6 Prognosis

Animals with congenital idiopathic megaesophagus have a fair prognosis. With adequate attention to caloric needs and prevention of aspiration pneumonia, many animals will develop improved esophageal motility over months. Pet owners must be committed to a prolonged period of physical therapy and nutritional support. The morbidity and mortality of acquired idiopathic megaesophagus continues to be unacceptably high.

131.4 VOMITING

131.4.1 Definition

Vomiting is the forceful ejection of upper gastrointestinal (GI) tract contents and may occur as a result of gastric, intestinal, or systemic disease.

131.4.2 Physiology of Vomiting

The vomiting reflex is mediated by the vomiting center in the medulla.[3] Vagal and sympathetic afferent pathways from the GI tract transmit impulses to the vomiting center when stimulated by inflammation or overdistention. The vomiting center also receives stimulation from within the brain; the vestibular system, cerebrum, and chemoreceptor trigger zone all provide input to the vomiting center. The latter is a specialized region, lacking an intact blood-brain barrier, that is located on the floor of the fourth ventricle. The chemoreceptor trigger zone is sensitive to several common drugs and toxins. The pathways involved in vomiting and the receptors involved are shown schematically in Figure 131-1.

Sufficient stimulation of the vomiting center results in the initiation of vomiting. A period of intestinal antiperistalsis is followed by a highly coordinated sequence of events, beginning with a deep inspiration and ending with a strong simultaneous contraction of the diaphragm and abdominal wall musculature and relaxation of the lower esophageal sphincter.

131.4.3 Clinical Consequences of Vomiting

The principal deleterious consequence of vomiting is dehydration as a result of fluid loss in the vomitus and a reduced fluid intake. The loss of GI contents compounded by dehydration may lead to electrolyte and acid-base disturbances. A hypochloremic metabolic alkalosis, primarily resulting from the loss of gastric contents rich in hydrogen and chloride ions, with or without a contraction alkalosis, is the most common finding in dogs with GI foreign bodies, regardless of their location.[4] Patients with more chronic vomiting may be more prone to developing metabolic acidosis as a result of dehydration, and mixed acid-base disorders may be seen. Hypokalemia is the most common electrolyte disturbance in vomiting patients. Aspiration pneumonia is a less common complication of vomiting than it is of regurgitation because reflex closure of the glottis occurs during emesis. It is a greater risk in animals with impaired laryngeal function, typically a result of primary laryngeal disease or a reduced state of consciousness.

131.4.4 Differential Diagnoses

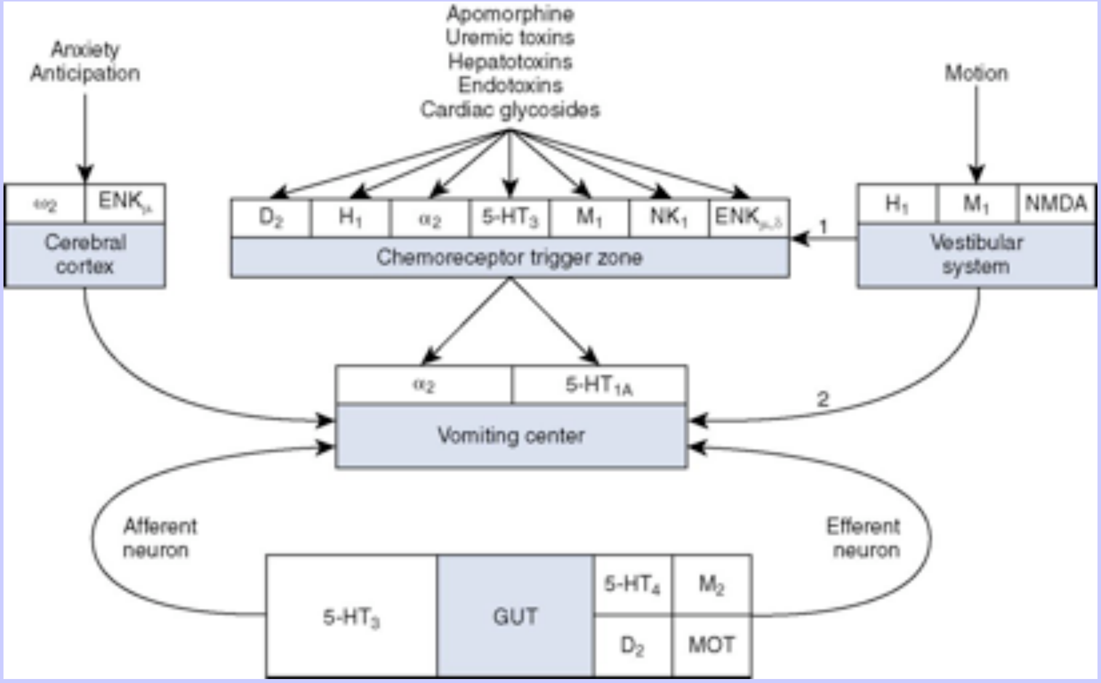
There are many differential diagnoses for vomiting, and to assist in the investigation and treatment it can be useful to subdivide these. One common subdivision is between those diseases in which the primary pathology is GI and those in which the primary pathology is extragastrointestinal. It can also be useful to distinguish between those diseases that are more likely to cause acute vomiting and those that are more likely to cause chronic vomiting. The most common and important differential diagnoses for vomiting are shown in Box 131-2. It is worthwhile to note that for the extragastrointestinal causes of vomiting, other systemic signs such as polydipsia or weight loss are likely to be present. Thus an animal that is vomiting but lacks other signs is more likely to have primary GI disease, and an animal that vomits only occasionally and yet has marked systemic signs is more likely to have an extragastrointestinal problem.

131.4.5 Diagnostic Approach

131.4.5.1 History

A description of the character of the vomiting should be obtained and, as described above, should be 572
distinguished from regurgitation. It is important to determine the approximate frequency and duration of 573
vomiting because the chronicity and severity of signs will aid in formulating a diagnostic and treatment plan. Fresh blood or digested blood ("coffee grounds") is suggestive of gastric ulceration, but bleeding is also often seen in acute infectious conditions such as the hemorrhagic gastroenteritis syndrome. Other important information from the patient's history includes vaccination status, travel history, medication history, dietary indiscretion or recent diet changes, drug or toxin exposure, and any possibility of foreign body ingestion. As noted above, systemic signs should raise the possibility of an extragastrointestinal cause for the vomiting.

Figure 131-1 Schematic representation of the receptors and pathways involved in vomiting. *1,* Pathway more important in dogs; *2,* pathway more important in cats. Receptors: *D,* dopaminergic; *H,* histaminergic; *M,* acetylcholine (muscarinic); *NK,* neurokinin; *5-HT,* serotonin; *α,* α-adrenergic; *ω,* benzodiazepine; *ENK,* enkephalinergic opioid; *MOT,* motilin; *NMDA,* glutamate.



131.4.5.2 Physical Examination

Vital signs and a thorough physical examination are important for the vomiting patient. The most important part of the physical examination is a thorough palpation of the abdomen. Attention should be paid to any abdominal pain or discomfort and the presence of any palpable effusion, organ distention, masses, or foreign bodies. The mouth should be examined for evidence of systemic disease (uremic or ketotic odor, ulcers) or a linear foreign body. In cats, the thyroid gland should be palpated to check for a goiter. A rectal examination should be performed for additional information (hematochezia, worms, prostatomegaly with or without pain), and an examination of the central nervous system may be indicated in difficult cases. Assessment of hydration and hemodynamic status will aid in formulating an appropriate treatment plan.

131.4.5.3 Clinical Pathology

A full hematology and biochemistry panel should be performed in any persistently vomiting patient. In most animals with an extragastrointestinal cause, there will be notable abnormalities in the biochemistry panel results. Normal biochemical and hematologic parameters are more strongly suggestive of primary GI disease. The hematology and biochemistry panels also allow evaluation of abnormalities in electrolytes and acid-base status, which may be complications of protracted vomiting. A sample for urinalysis should be obtained at the earliest opportunity to aid with the differentiation of prerenal and renal azotemia. A fecal sample should be submitted for zinc sulfate flotation in all cases, and also for selective bacterial culture or analyses in patients with acute vomiting. Further testing should be performed based on clinical suspicions.

131.4.5.4 Diagnostic Imaging

Radiography and abdominal ultrasonography are vital in the investigation of vomiting. The preferred diagnostic imaging modality depends on the nature of the complaint. In the acutely vomiting patient, abdominal radiographs are generally preferred over ultrasonography because they have adequate sensitivity and greater specificity for detecting intestinal obstruction. As such, they can be used to help determine whether medical or surgical management of the case is more appropriate. The role of abdominal ultrasonography in the acutely vomiting patient is more limited; it may be useful in the evaluation of neoplastic obstructions and other abdominal organs if an extragastrointestinal cause of the vomiting is suspected. If radiography and ultrasonography are equivocal and GI obstruction is still suspected, administration of barium and sequential abdominal radiographs may be helpful.

In patients with chronic vomiting, the likelihood of intestinal obstruction is much less than in patients who are vomiting acutely, and abdominal radiography has a lower diagnostic yield. Abdominal ultrasonography is generally preferred in these patients. It allows an evaluation of the intestinal wall thickness and layering along 573 574 with a thorough evaluation of the extraintestinal structures. It therefore proves very useful in helping to decide whether medical management, endoscopy, or surgery would be most appropriate.

131.4.5.4.1

Box 131-2 Important Differential Diagnoses for Vomiting

131.4.5.4.1.1

Gastrointestinal

131.4.5.4.1.1.1

Obstruction

- Foreign body*
- Intussusception*
- Neoplasia
- Torsion or volvulus

131.4.5.4.1.1.2

Dietary

- Allergy†
- Intolerance†
- Indiscretion*

131.4.5.4.1.1.3

Infectious

- Viral (parvovirus)*
- Parasitic†
- Bacterial (salmonellosis)*

131.4.5.4.1.1.4

Other

- Neoplasia†
- Inflammatory bowel disease†
- Gastrointestinal ulceration

- NSAID-induced
- Uremic gastritis
- Liver disease
- Idiopathic

131.4.5.4.1.2

Extragastrointestinal

- Uremia
- Pancreatitis*
- Diabetic ketoacidosis*
- Liver disease
- Peritonitis*
- Pyometra*
- Prostatitis
- Drug or toxin induced*
- Hypoadrenocorticism†
- Hyperthyroidism
- Vestibular disease
- Heartworm disease (cats)

NSAID, Nonsteroidal antiinflammatory drug.

* More commonly acute.

† More commonly chronic.

Thoracic radiographs should also be obtained in vomiting patients. Their role is multifold. They may show evidence of esophageal disease if the history has led to an incorrect identification of the primary problem as vomiting, they aid in the detection of neoplastic involvement in the thorax, and they may show evidence of aspiration pneumonia.

131.4.6 General Treatment Guidelines

The important factors to consider when treating a vomiting patient are: (1) treatment of the underlying cause, (2) treatment and prevention and electrolyte and acid-base disturbances, and (3) symptomatic control of further vomiting, when appropriate. Fluid therapy and antiemetic drugs are discussed in Chapters 55, 56, 181, 182, Potassium Disorders, Calcium Disorders, Gastrointestinal Protectants, and Antiemetics, respectively. The general recommendation is to withhold food for 24 to 48 hours after the last episode of vomiting.[5] The rationale for this is to avoid stimulating further vomiting, to avoid the development of food aversions in nauseated patients, and to reduce the risk of aspiration pneumonia.

Food should always be withheld from any patient with suspected GI obstruction or any patient whose signs worsen after feeding. However, some vomiting patients may have a significantly quicker recovery when early enteral nutrition is instigated, and dogmatic enforcement of starvation may be unnecessary for some canine and feline patients.[6] Animals with persistent vomiting may not be good candidates for feeding tubes, and parenteral nutrition may be necessary (see Chapter 14, Parenteral Nutrition).

131.5 SUGGESTED FURTHER READING*

AR Gaynor, FS Shofer, RJ Washabau: Risk factors for acquired megaesophagus in dogs. *J Am Vet Med Assoc*. **211**, 1997, 1406, *A retrospective, case-control study that is the only epidemiologic investigation of the risk factors for canine megaesophagus, which include peripheral neuropathies, laryngeal paralysis, myasthenia gravis, and esophagitis. No association found between hypothyroidism and megaesophagus.*

RJ Washabau: Gastrointestinal motility disorders and gastrointestinal prokinetic therapy. *Vet Clin North Am Small Anim Pract*. **33**, 2003, 1007, *A review of gastrointestinal motility disorders that provides a brief summary of the pathogenesis, clinical signs, and treatment of canine idiopathic megaesophagus.*

C Webb, DC Twedt: Canine gastritis. *Vet Clin North Am Small Anim Pract*. **33**, 2003, 969, *An extensive review article that discusses the pathogenesis, investigation, and treatment of gastric inflammation. Discusses a wide range of conditions, reflecting the diverse causes of vomiting in canine patients.*

* See the CD-ROM for a complete list of references

132 Chapter 132 Diarrhea

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132.1 KEY POINTS

- Diarrhea is a common clinical finding in critically ill animals.
- Diarrhea can lead to abnormalities in nutrient, acid-base, and electrolyte balance.
- Diarrhea may result from iatrogenic causes, primary gastrointestinal diseases, or other disease processes.

132.2 INTRODUCTION

Diarrhea is a very common clinical sign observed in critically ill canine and feline patients. Diarrhea is defined as an increase in fecal mass caused by an increase in fecal water or solid content. This is usually associated with an increase in frequency, fluidity, or volume of feces. In a 20-kg dog, approximately 2.5 L of fluid enters the duodenum each day, and about 98% of the fluid entering the intestine is absorbed.[1] Diarrhea in the critical care setting is often overlooked and overshadowed by the primary disease process. However, diarrhea can lead to severe aberrations in nutrient, acid-base, fluid, and electrolyte balance. Without proper attention it can lead to the deterioration of the patient's condition. Diarrhea may be associated with patient discomfort, local dermatitis, catheter or catheter site infections, and potentially bacterial translocation if the integrity of the intestinal mucosa is altered. Consideration of the most likely cause is important because it allows the clinician to decide which diagnostic modalities are indicated for proper investigation of the diarrhea. Three broad etiologic categories may be used when considering diarrhea: iatrogenic causes, primary gastrointestinal (GI) causes, and other diseases secondarily causing diarrhea.

132.3 PATHOPHYSIOLOGIC MECHANISMS OF DIARRHEA

There are several categorization schemes for diarrhea, with great overlap among the classifications. One of the most commonly used classification schemes arranges the pathophysiologic mechanisms underlying diarrhea as follows: osmotic diarrhea, secretory diarrhea, diarrhea resulting from altered permeability, and diarrhea resulting from deranged motility.

Osmotic diarrhea is caused by the presence of excess luminal osmoles, leading to fluid retention and fluid draw into the intestinal lumen. Most causes of a diarrhea have an osmotic component.

Secretory diarrhea is caused by a net increase in intestinal fluid secretion. This results from either an absolute increase in intestinal secretion or a relative increase caused by a decrease in intestinal absorption.

Normal intestinal physiology and systemic health are dependent on the semipermeable nature of the intestinal mucosa. Nutrients, electrolytes, and fluid are absorbed and secreted, and the mucosa and immune system of the intestine inhibit translocation of bacteria and bacterial toxins. However, microscopic and macroscopic damage to either the epithelial cells or epithelial cell junctions can lead to altered intestinal permeability. Not only are vital substances lost into the intestinal lumen, but the altered permeability leaves the intestine vulnerable to translocation of potentially fatal bacteria and their products.

Alterations in intestinal motility are probably the least understood of the causes of diarrhea. Motility alterations leading to diarrhea include either increased peristaltic contractions or decreased segmental contractions.[1] Even within this classification scheme, significant overlap occurs among the groups.

In animals with primary GI causes of diarrhea, historical questions may provide evidence that allows anatomic localization of the disease to either the small or large bowel. This differentiation will allow a more accurate formation of differential diagnoses and subsequent diagnostic testing. Historical and clinical differences usually noted between small and large bowel diarrhea are illustrated in Table 132-1.

132.4 IATROGENIC CAUSES OF DIARRHEA

Iatrogenic causes of diarrhea are likely more common than is realized and should be ruled out to facilitate clinical improvement. Diarrhea is a common side effect of several classes of drugs used in critically ill patients (Box 132-1). Antimicrobial agents may cause diarrhea as a direct result of drug formulation or properties, or as a result of alterations in intestinal microbacterial flora. Most of the chemotherapeutic agents have direct toxic effects against the rapidly dividing cells of the intestinal crypts, leading to villous blunting and altered absorption. Other classes of drugs such as antiarrhythmic agents, lactulose, and proton pump inhibitors may also be associated with diarrhea.

Acute or abrupt changes in the diet are not uncommon in hospitalized or critically ill patients. Anorexic animals are often coaxed to eat with canned diets and other potentially novel foods. Enteral tube feeding is commonly employed in critically ill patients. The osmotic and caloric properties of these diets may exceed the digestive and absorptive capacities of the intestine and lead to osmotic diarrhea. Furthermore, prolonged quiescence of the intestine from either anorexia or parenteral nutrition can lead to villous atrophy and decreased absorptive function when enteral feeding is initiated.

Table 132-1 Differentiation of Diarrhea Based on Anatomic Location

Characteristic	Small Bowel	Large Bowel
Mucus	Uncommon	Common
Hematochezia	Uncommon	May be present
Stool volume	Increased to normal	Normal to decreased
Melena	May be present	Absent
Frequency	May be increased to normal	Increased
Urgency	Uncommon	Common
Tenesmus	Uncommon	Common

132.4.1 Box 132-1 Medications Commonly Associated With Diarrhea[17,18]

132.4.1.1 Antimicrobial Agents

132.4.1.1.1 Gastrointestinal Medications

Histamine-2 blockers

Misoprostol

Proton pump inhibitors

Oral antacids

132.4.1.2 Chemotherapeutic Agents

132.4.1.2.1 Cardiac Medications

Quinidine

Procainamide

Digoxin

132.4.1.2.2 Antihypertensive Agents

β-Blockers

ACE inhibitors

132.4.1.2.3 Immunomodulatory Agents

Azathioprine

Cyclophosphamide

Cyclosporine

132.4.1.2.4 Endocrine Medications

- Mitotane
- Trilostane
- Methimazole
- Acarbose

132.4.1.3 NSAIDs

132.4.1.3.1 Miscellaneous Agents

- Amitriptyline
- Parasiticides
- Bethanechol
- Clomipramine
- Colchicine
- Acetazolamide

ACE, Angiotensin-converting enzyme; *NSAIDs,* nonsteroidal antiinflammatory drugs.

132.5 PRIMARY GASTROINTESTINAL CAUSES OF DIARRHEA

Adverse reactions to foods can result from immunologic reactions (food allergy) or nonimmunologic reactions (food intolerance) to a dietary substance.[2] Although true food allergies are rare, food intolerance is probably one of the more common causes of acute diarrhea in the small animal patient. Intolerance can result from dietary indiscretion or gluttony, but often the exact cause is unknown. The resultant diarrhea is short term and self-limiting.

Infectious disease is a common cause of diarrhea in canine and feline patients. Gastrointestinal (GI) parasitism (e.g., *Ancylostoma, Toxocara* spp, *Toxascaris, Trichuris*) is another common cause of diarrhea, but is rarely associated with debilitation except in young or small patients. The exact role of various infectious bacterial organisms as the cause of diarrhea is controversial. GI disease and diarrhea may be associated with a variety of bacteria, including *Salmonella* spp, *Campylobacter* spp, enteropathogenic *Escherichia coli, Clostridium difficile,* and *Clostridium perfringens*. [3,4] Although diarrhea has been associated with clostridial organisms in the dog and cat,[3-5] the direct role remains unclear given that *C. difficile* toxin and *C. perfringens* enterotoxin can be demonstrated in the feces of animals with normal stool quality and no clinical GI signs.[6,7]

Systemic viral infections such as canine parvovirus and feline panleukopenia are commonly associated with diarrhea. Feline panleukopenia and canine parvovirus are caused by similar, but not identical, nonenveloped DNA parvoviruses.[8,9] Transmission occurs via oronasal exposure and the organism subsequently spreads to the bone marrow, lymphoid organs, and intestinal crypts, leading to a peripheral leukopenia and intestinal villus blunting and collapse.[8,9]

Fungal (*Histoplasma, Pythium, Cryptococcus* spp), algal *(Prototheca),* protozoal (*Tritrichomonas foetus, Giardia, Cryptosporidium, Isospora* spp), and rickettsial (*Neorickettsia* spp) gastroenteritis may be seen depending on the geographic location and husbandry of the patient. Intussusceptions may occur secondary to infectious or idiopathic causes, and may lead to severe diarrhea.

The role of small intestinal bacterial overgrowth (SIBO) or antibiotic-responsive diarrhea (ARD) is a controversial subject in small animal veterinary gastroenterology. Debate exists not only regarding whether the disease occurs as a primary condition, but also in how it should be defined and how it is best diagnosed. Some authors have divided the disease into either secondary SIBO in the cases in which an accompanying or primary intestinal disease can be identified, or idiopathic ARD in the cases in which no underlying disease can be found.[10] Examples of secondary SIBO can be seen with exocrine pancreatic insufficiency and inflammatory bowel disease (IBD). The exact etiology of ARD has yet to be identified, but local intestinal immunodeficiency may play a role in the pathogenesis.[11]

Neoplastic disease may also lead to diarrhea in small animals patients; GI adenocarcinoma, alimentary lymphosarcoma, mast cell tumor, and GI stromal tumors are examples. These tumors may cause significant intestinal protein and blood loss.

IBD is one of the more common causes of chronic diarrhea in cats and dogs. Loss of local immune tolerance to normal dietary and bacterial components leads to up-regulation of immune and inflammatory responses and establishment of an inflammatory focus within the intestine. Infiltration with inflammatory cells leads to thickening of the intestinal absorptive surface and decreased absorptive capacity. There are different types of IBD in the dog and cat, and classification is based on the primary type of inflammatory cell infiltrate. Lymphocytic-plasmacytic is 576 the most common form of IBD, 577 but eosinophilic and granulomatous forms may also be diagnosed. Prolonged or extensive bowel disease can lead to severe metabolic derangements, including panhypoproteinemia and hypocholesterolemia. The diagnosis of IBD is based on histopathologic evidence of moderate to severe GI inflammation coupled with the exclusion of an underlying cause of the inflammation.

Lymphangiectasia can occur as a primary disease (Yorkshire Terrier, Norwegian Lundehund, and Maltese Terrier) or secondary to other infiltrative processes such as IBD. Alterations of intestinal lymphatic permeability leads to leakage of protein-rich and fat-rich chyle into the intestinal lumen and loss of these dietary components into the feces. Resultant clinical signs include chronic diarrhea and severe weight loss.

132.6 EXTRAGASTROINTESTINAL DISEASES CAUSING DIARRHEA

Diarrhea may occur in dogs and cats with hepatobiliary disease for several reasons. Concurrent inflammatory GI disease may be seen in the dog and is common in the cat.[12-14] End-stage cirrhosis may be associated with elevated portal hydrostatic pressures, and functional hepatic failure may lead to hypoalbuminemia and GI wall edema. Both of these conditions often lead to altered absorptive properties of the gut. Diseases affecting the biliary tree may also hinder delivery of bile salts to the intestine, leading to fat maldigestion.

Diarrhea is commonly seen as a sequela of pancreatic disease. Exocrine pancreatic insufficiency may result from pancreatic acinar atrophy (dogs more commonly) or chronic pancreatitis (cats more commonly). Lack of exocrine pancreatic function leads to maldigestion and malabsorption of dietary substrates and culminates in diarrhea and weight loss. Both acute and chronic pancreatitis may also lead to diarrhea. Pancreatic inflammation may cause local inflammation of the duodenum and colon, interfere with pancreatic acinar secretion, and result in decreased bile salt delivery to the small intestine via obstruction of biliary flow.

Congestive heart failure, particularly right-sided failure, can lead to intestinal and hepatic venous congestion and ascites. Congestion of the splanchnic vasculature may lead to altered absorptive capacities of the intestine.

Several endocrine disorders may be associated with diarrhea. Diarrhea is noted in some cats with hyperthyroidism. The diarrhea in these cases may be a result of increased food intake as well as intestinal hypermotility. Waxing and waning GI signs are seen frequently in dogs and less commonly in cats with hypoadrenocorticism. Cortisol is vital for maintenance of normal GI function, motility, and integrity, as well as vascular tone and subsequent perfusion. The lack of mineralocorticoids may be associated with alterations in electrolyte balance, leading to altered GI motility and absorption. Diarrhea is an uncommonly reported clinical sign associated with hypothyroidism.

Various other diseases may be associated with diarrhea. Idiopathic noncirrhotic portal hypertension may interfere with absorption within the intestinal tract. The role of hypoalbuminemia as a direct cause of diarrhea is debated. The decreased oncotic draw resulting from hypoalbuminemia leads to alterations in Starling forces and decreased absorption of fluid across the intestinal lumen. Hemorrhagic diarrhea is seen commonly in critically ill patients suffering from or following resuscitation from various causes of cardiovascular shock, such as following an episode of heat-induced illness. GI complications are common in animals with acute and chronic renal disease, but diarrhea is not commonly reported. Systemic infections (including sepsis) may secondarily affect the GI tract and cause diarrhea. Experimental canine studies have shown that bacterial endotoxin impairs colonic water and sodium absorption and increases small and large intestinal motility, at least partially explaining the diarrhea noted in septic patients.[15,16]

132.7

DIAGNOSTIC EVALUATION

The diagnostic evaluation of diarrhea is best guided by the historical, clinicopathologic, and physical examination findings. The physical condition of the patient and the duration and clinical course of the diarrhea will help determine how aggressive the clinician should be in attempting to find a cause.

Results of a complete blood count, serum chemistry profile, and urinalysis are indicated in all critically ill patients and often help to delineate between GI and non-GI causes of diarrhea. Based on these findings, additional tests may be needed to screen for hyperthyroidism, hypoadrenocorticism, or occult liver disease. Fecal flotation (including zinc sulfate for *Giardia*) and direct cytologic examination of the feces is recommended in most cases. Although cytologic examination of the feces may help indirectly to point toward a particular pathogen, isolation or amplification of toxin or enterotoxin may provide a more specific diagnosis in the case of clostridial infection. Bacterial culture (*Salmonella, Campylobacter,* enteropathogenic *E. coli*), enterotoxin screening *(Clostridium)*, and enzyme-linked immunosorbent assay (ELISA) (parvovirus) of the feces may be indicated when an infectious cause is suspected. Specific tests for other infectious agents may also be indicated depending on the geographic location and husbandry of the patient. Exfoliative rectal cytology may be useful in diagnosing fungal, algal, inflammatory, and neoplastic diseases. Trypsin-like immunoreactivity testing is indicated in any patient with suspected exocrine pancreatic insufficiency. Folate and cobalamin testing may be helpful in animals suffering from SIBO. Although abdominal radiographs are of limited value in animals primarily affected with diarrhea, abdominal ultrasound is often indicated and useful for assessing integrity, architecture, and thickness of the GI system and other abdominal organs. Lastly, GI endoscopy or exploratory laparotomy is often needed for direct visualization of the intestinal tract and procurement of diagnostic samples.

132.8 TREATMENT

Iatrogenic causes of diarrhea should be considered in all patients, especially those in which diarrhea was not part of the presenting complaint. If the diarrhea is severe, therapeutic medications may need to be discontinued or modified. Although diarrhea is commonly associated with enteral feeding, the diet formulation may need to be altered if the diarrhea is severe or adversely affecting the patient's quality of life.

Treatment of diarrhea associated with primary GI diseases or diseases secondarily causing diarrhea is best achieved after careful diagnostic evaluation of the underlying cause. After a definitive diagnosis has been achieved, direct treatment can be initiated. Rarely, medications directed toward symptomatic treatment of the diarrhea are used (see Chapter 181, Gastrointestinal Protectants). Intestinal transit time is effectively a result of the balance between propulsive peristalsis and segmental contractions.[1] Contrary to historical belief, diarrhea rarely results from increased peristalsis, but more commonly is the result of decreased segmental contractions.[1] Anticholinergic agents generally are contraindicated because they decrease both propulsive peristalsis and segmental contractions and predispose the patient to ileus. Conversely, opioid-containing medications such as loperamide, diphenoxylate, and opium tincture can decrease propulsive contractions and increase segmental contractions, as well as increasing water and fluid absorption.[1] These medications may be indicated in some cases of diarrhea in which infectious causes have been excluded. Kaolin, pectin, and bismuth subsalicylate are used occasionally for symptomatic treatment.[1] Symptomatic therapy is rarely indicated because treatment of the primary disease process provides the best means for eliminating diarrhea. Indications for symptomatic therapy include diarrhea that adversely affects the patient's quality of life, causes severe fecal scalding of the skin, or predisposes to secondary infection (e.g., urinary or intravenous catheter infections in recumbent animals).

In animals with IBD, treatment often is tailored to the individual patient given severity of the clinical signs and histopathologic lesions. Dogs and cats with intermittent clinical signs, good body condition, and mild histologic lesions may respond to dietary therapy alone. The rationale behind dietary therapy in the treatment of IBD is that the loss of immunologic tolerance to normal dietary proteins and subsequent GI inflammation may be one of the pathophysiologic mechanisms behind the disorder. Dietary therapy for IBD usually relies on either a novel protein diet or a diet using a hydrolyzed protein source. Animals with some degree of lymphangiectasia may benefit from a low-fat diet.

However, most animals with moderate to severe disease will need some degree of immunomodulation to obtain clinical remission. Glucocorticoids (prednisone, prednisolone, and dexamethasone) are the mainstay of immunomodulatory therapy. There has been interest in the locally active steroid, budesonide. This drug undergoes significant first-pass metabolism, thereby limiting systemic absorption and potentially lessening the side effects compared to glucocorticoids. Azathioprine, chlorambucil, or other immunomodulating agents may be needed in dogs with refractory disease or those unable to tolerate glucocorticoids. Aminosalicylates (sulfasalazine, mesalamine) can be used in dogs with primarily large bowel disease. Metronidazole is often used for both its antimicrobial and antiinflammatory effects.

Antibiotic therapy may be useful in many other diarrheal diseases of dogs and cats (Table 132-2). Primary (idiopathic) or secondary ARD will often respond well to antimicrobial agents. Those most often used include metronidazole, oxytetracycline, and tylosin.[4] The drug of choice for treatment of *Campylobacter* spp is the macrolide erythromycin. However, its use is associated with GI side effects (typically vomiting and/or diarrhea). Other antimicrobial drugs that may be considered include enrofloxacin, tetracyclines, chloramphenicol, cefoxitin, and tylosin. Animals with diarrhea of suspected clostridial origin may be treated with metronidazole, ampicillin, macrolides, or tetracyclines.[4]

Table 132-2 Formulary of Commonly used Drugs for the Treatment of Diarrhea in Small Animals

Drug	**Canine**	**Feline**
Prednisone	1 to 2 mg/kg PO q12h	1 to 4 mg/kg PO q12h
Budesonide	<5 kg: 1 mg PO q24h 5 to 15 kg: 2 mg PO q24h>15 kg: 3 mg PO q24h	1 mg PO q24h
Azathioprine	2 mg/kg PO q24h	Not routinely used
Chlorambucil	Not routinely used	2 mg/m^2 PO q48h
Sulfasalazine	10 to 15 mg/kg PO q8-12h	10 to 20 mg/kg PO q24h
Metronidazole	10 to 15 mg/kg PO q12h	10 to 15 mg/kg PO q12h
Oxytetracycline	22 mg/kg PO q8h	10 to 15 mg/kg PO q8h
Tylosin	10 to 20 mg/kg PO q8-12h	10 to 20 mg/kg PO q8-12h
Erythromycin	10 to 20 mg/kg PO q8h	10 to 20 mg/kg PO q8h
Enrofloxacin	10 to 20 mg/kg PO q24h	5 mg/kg PO q24h

PO, Per os.

132.9

SUGGESTED FURTHER READING*

NJ Cave, SL Marks, PH Kass, et al.: Evaluation of a routine diagnostic fecal panel for dogs with diarrhea. *J Am Vet Med Assoc*. **221**, 2002, 52, *A case-controlled study examining the diagnostic yield of fecal panels in the evaluation of canine diarrhea.*

CE Greene: Enteric bacterial infections. In CE Greene (Ed.): *Infectious disease of the dog and cat*. ed 3, 2006, Saunders, St Louis, *The most detailed reference available focusing on small animal infectious disease.*

EJ Hall, AJ German: Disease of the small intestine. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. 2005, Saunders, St Louis, *Up-to-date chapter reviewing common diseases of the canine and feline small intestine.*

* See the CD-ROM for a complete list of references

133 Chapter 133 Peritonitis

Susan W. Volk, VMD, PhD, DACVS

133.1 KEY POINTS

- Peritonitis is inflammation of the peritoneal cavity and is most commonly the result of gastrointestinal rupture, perforation, or dehiscence in small animals.
- Clinical signs in patients with peritonitis may be mild to severe and are often nonspecific.
- Abdominocentesis is the diagnostic method of choice for confirming peritonitis.
- Abdominal fluid cytology that reveals degenerative neutrophils and intracellular bacteria confirms a diagnosis of septic peritonitis and is an indication for emergency surgical exploration of the abdomen.
- Open peritoneal drainage or closed suction drainage should be considered for cases of septic peritonitis in which the source of contamination cannot be controlled completely or if significant contamination or inflammation remains following surgical debridement and lavage.
- Prognosis is guarded in patients with peritonitis. Reported survival rates are highly variable and dependent on the etiology and presence of infection.

133.2 INTRODUCTION

Peritonitis is defined as inflammation of the peritoneal cavity and may be classified according to the underlying etiology (primary or secondary), extent (localized or generalized), or the presence of infectious agents (septic or nonseptic). Primary peritonitis refers to a spontaneous inflammatory condition in the absence of underlying intraabdominal pathology. Secondary peritonitis occurs more commonly and is the consequence of a preexisting aseptic or septic pathologic, intraabdominal condition. Secondary septic peritonitis is the more common form in the dog and cat, most commonly resulting from leakage of gastrointestinal (GI) contents from a compromised GI tract. Because of the multitude of conditions that may lead to peritonitis, the types of clinical signs and their severity are varied.

Hematogenous dissemination of infectious agents has been postulated as the mechanism of development of primary peritonitis and is likely facilitated by impaired host immune defenses. The most common form of primary peritonitis is the effusive form of feline infectious peritonitis, caused by feline coronavirus, which should be included on any differential diagnosis list for cats with peritoneal effusion. Other infectious agents reported to have caused primary peritonitis in dogs and cats include *Salmonella typhimurium, Chlamydia psittaci, Clostridium limosum, Mesocestoides* spp, *Blastomyces* spp, and *Candida* spp.

Inflammation of the abdominal cavity in the absence of infectious pathogens (aseptic peritonitis) most commonly occurs in response to exposure of the peritoneum to sterile fluids (i.e., gastric, biliary, or urine), pancreatic enzymes, or foreign material. Aseptic bile and urine cause minimal peritoneal inflammation, and gastric fluid and pancreatic enzyme leakage lead to a more intense peritoneal reaction. Both microscopic and macroscopic foreign material, including surgical glove powder, surgical materials (suture, cotton swabs, surgical sponges), hair, and impaled objects (sticks, plant material, metal) may elicit a granulomatous response. To minimize iatrogenic causes of aseptic peritonitis, it is recommended that the surgeons rinse or wipe surgical gloves with sterile saline or use powder-free gloves, perform a surgical sponge count before opening and closing a celiotomy, and use surgical sponges with radiopaque markers.

More commonly, secondary peritonitis can be identified as a septic process, with the most frequent source of infection being the GI tract. Leakage of GI contents may occur through stomach and intestinal walls that have been compromised by ulceration, foreign body obstruction, neoplasia, trauma, ischemic damage, or dehiscence of a previous surgical incision. Spontaneous gastroduodenal perforation may be associated with nonsteroidal antiinflammatory drug administration but may also be seen with corticosteroid administration, neoplastic and nonneoplastic GI infiltrative disease, gastrinoma, and hepatic disease.[1,2] GI linear foreign bodies in dogs have been reported to lead to the development of peritonitis in 41% of cases, higher than that previously reported for cats.[3] Dehiscence occurs in 7% to 16% of postoperative patients requiring intestinal enterotomy or anastomosis, with mortality rates of 75% to 85% in this population. One study identified dogs as being at high risk for leakage following intestinal anastomosis if they had two or more of the following conditions: preoperative peritonitis, intestinal foreign body, and a serum albumin concentration of 2.5 g/dl or less.[4] Other causes of septic peritonitis can be found in Box 133-1.

133.3 CLINICAL SIGNS

Historical information may provide clues regarding the underlying cause of peritonitis. Previous and current maladies and surgical procedures (including neutering), current medications (particularly those which may predispose to GI ulceration), and duration of current clinical signs should be investigated. Owners should be questioned specifically regarding potential for trauma exposure and foreign body ingestion.

Clinical signs of dogs and cats with peritonitis vary in both type and intensity and may reflect the underlying disease process. Peritoneal effusion is a consistent finding but may be difficult to appreciate on physical examination if a small volume of fluid is present, and may even be difficult to detect sonographically in animals 579 exhibiting dehydration. 580 Abdominal pain may be appreciated on palpation, with a small number of dogs exhibiting the “prayer position” in an attempt to relieve abdominal discomfort. In a retrospective study focusing on cats with septic peritonitis, only 62% exhibited pain on palpation of the abdomen.[5] Most animals with septic peritonitis are systemically ill and exhibit nonspecific clinical signs such as anorexia, vomiting, mental depression, and lethargy. It should be noted that animals with uroperitoneum may continue to urinate with a concurrent leakage into the peritoneal cavity. These patients may arrive in progressive states of hypovolemic and cardiovascular shock, with either injected or pale mucous membranes, prolonged capillary refill time, tachycardia with weak pulses, and with either hyperthermia or hypothermia reflecting poor peripheral perfusion. A significant number of cats (16%) with septic peritonitis exhibited bradycardia[5] (see Chapter 106, Sepsis).

133.3.1 Box 133-1 Differential Diagnoses of Septic Peritonitis

133.3.1.1 Primary

GDV, Gastric dilatation-volvulus.

Feline coronavirus (feline infectious peritonitis)

Salmonella typhimurium

Chlamydia psittaci

Clostridium limosum

Mesocestoides spp

Blastomyces spp

Candidiasis spp

133.3.1.2 Secondary

Penetrating abdominal wounds

Surgical peritoneal contamination

Peritoneal dialysis

Gastrointestinal conditions

Gastric rupture secondary to GDV, neoplasia, perforating ulcer

Intestinal leakage

Perforating foreign body, ulcer, or neoplasia

Bacterial translocation secondary to obstruction (foreign body, neoplasia, intussusception, or bowel incarceration)

Dehiscence of intestinal surgical wound

Ischemic intestinal injury

Hepatobiliary condition

Liver abscess

Liver lobe torsion with abscess formation

Ruptured biliary tract with bacterobilia

Pancreatitis or pancreatic abscess

Hemolymphatic conditions

Splenic abscess

Splenic torsion with anaerobic bacterial colonization

Mesenteric lymph node abscess formation

Urogenital conditions

Renal abscess

Septic uroabdomen

Pyometra (ruptured or with mural bacterial translocation)

Uterine torsion

Prostatic abscess formation

133.4 DIAGNOSTIC TESTS

Patients with suspected or confirmed peritonitis should have routine hematologic, biochemical, and coagulation analyses. A marked neutrophilia with a left shift is the predominant hematologic finding, although a normal or low neutrophil count may be present. It is anticipated that animals recovering without incident from GI surgery may also have a transient inflammatory leukogram; however, the overall peripheral white blood cell counts typically fall within normal limits.[6] An increasingly left-shifted neutrophilia (or neutropenia) paired with clinical signs of peritonitis may raise the clinician's index of suspicion for postoperative intestinal dehiscence (which typically occurs 3 to 5 days postoperatively).

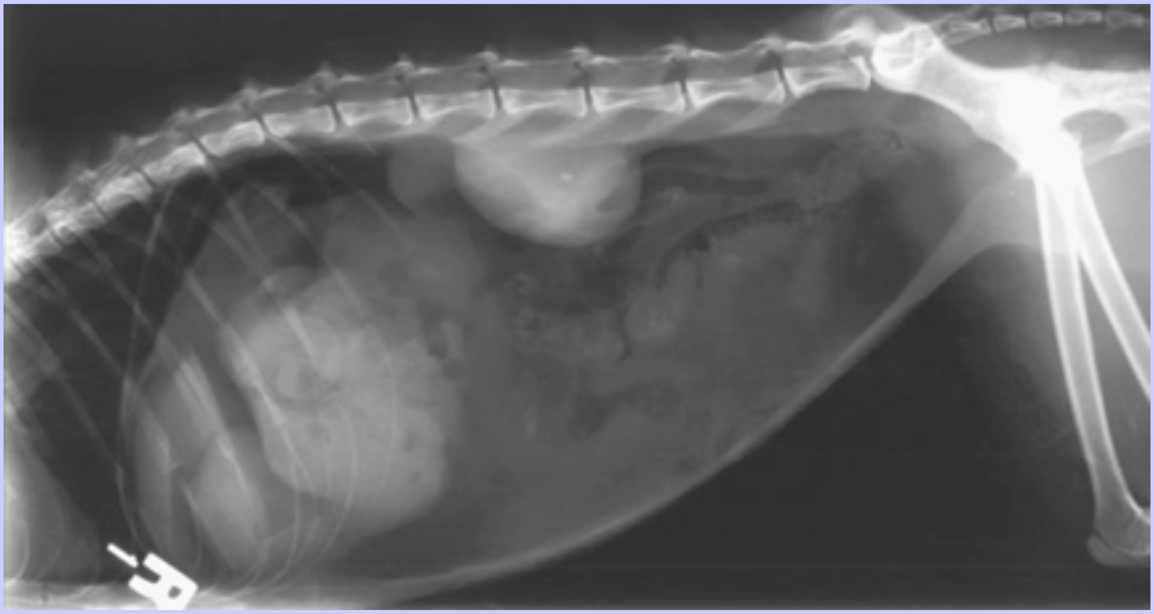
Furthermore, acid-base and electrolyte abnormalities may be noted. Hyperkalemia may indicate uroperitoneum, particularly if trauma or urinary tract dysfunction has been noted historically. Hypoproteinemia may be a result of the loss of protein within the peritoneal cavity. Patients with a concurrent septic process may be hypoglycemic. Hepatic enzymes, creatinine, and blood urea nitrogen may be elevated, indicating primary dysfunction of these organs or perhaps reflecting states of decreased perfusion or dehydration. The serum of patients with bile peritonitis may be icteric if the total bilirubin is elevated.

Patients with suspected peritonitis should be evaluated for peritoneal effusion. Little or no fluid may be detected initially if patients arrive early in the disease process or before fluid resuscitation if they are dehydrated. Large volumes of effusion may be obtained via blind abdominocentesis or, alternatively, via ultrasonographic guidance. Single paracentesis attempts are successful in only 20% of patients with low volumes of peritoneal effusion (3 ml/kg) and in only 80% with larger volumes (10 ml/kg). Ultrasonographic guidance will facilitate the retrieval of smaller volumes of peritoneal fluid. If single-site sampling is negative for fluid, four-quadrant sampling should be performed.

A diagnostic peritoneal lavage should be performed when peritonitis is suspected despite the absence of detectable effusion or when a minimal volume of effusion makes it difficult to obtain a sample. Diagnostic peritoneal lavage ideally is performed using a peritoneal dialysis catheter but can also be performed using an over-the-needle, large-bore (14 to 16 gauge) catheter. The technique is performed by infusion of 22 ml/kg of a warmed, sterile isotonic saline solution through the catheter inserted in an aseptically prepared site just caudal to the umbilicus and retrieval of a sample for analysis and culture and sensitivity. It is important to remember that the lavage solution will dilute the sample and therefore may alter the analysis. A repeated diagnostic peritoneal lavage may increase accuracy of the technique when results of the first procedure are equivocal (see Chapter 156, Diagnostic Peritoneal Lavage).

Leukocyte counts in peritoneal fluid are normally less than 500 cells/µl. White blood cell counts between 1000 and 2000 cells/µl indicate mild to moderate inflammation, and a higher peritoneal fluid leukocytosis suggests marked peritonitis.[6,7] However, cell counts in peritoneal lavage fluid obtained from postoperative patients undergoing intestinal resection and anastomosis may also show evidence of significant inflammation in the absence of surgical complications. In the patient that has undergone a celiotomy, 7000 to 9000 cells/µl suggests mild to moderate peritonitis. In these patients, intracellular bacteria or increasing inflammation (numbers of neutrophils or morphologic features of toxicity in these cells) observed in serial samples correlated with clinical findings may prove more useful than single leukocyte counts in abdominocentesis samples when deciding whether reoperation is indicated. It is also of note that dogs receiving antibiotics may have no observable bacteria in peritoneal fluid samples, despite having peritoneal contamination.

Figure 133-1 Lateral abdominal radiograph showing free peritoneal gas and possibly ingesta free within the abdomen. Pneumoperitoneum without a history of recent surgery or open-needle abdominocentesis indicates the need for abdominal exploratory. This cat was diagnosed with a ruptured gastric mass during surgery.



In addition to the presence of bacteria and a high nucleated cell count, the glucose concentration of abdominal effusion is a useful predictor of bacterial peritonitis in dogs. A concentration difference of more than 20 mg/dl between paired samples for blood and peritoneal fluid glucose is a reliable predictor of a bacterial peritonitis. Additionally, a blood-to-fluid lactate difference less than 2 mmol/L was predictive of septic peritonitis in dogs but has not been as useful in cats.[8,9] Intravenous administration of dextrose or the presence of a hemoperitoneum may decrease the accuracy of this test.

Samples for aerobic and anaerobic cultures should be obtained at the time of initial sampling so that additional samples are not required after confirming the presence of a septic process and initiating antibiotic therapy.

The diagnosis of uroperitoneum in dogs can be made if the peritoneal fluid creatinine or potassium concentration exceeds that of the serum creatinine (>2:1) or potassium concentration (>1.4:1).[10] Similarly, biliary rupture will lead to a bilirubin concentration that is higher in the peritoneal fluid than in the serum. In addition, bile pigment or crystals may be visible on cytologic examination of the peritoneal effusion in animals with bile peritonitis (Color Plate 133-1). These changes may not be seen in patients with bile peritonitis secondary to a ruptured gallbladder mucocele because the gelatinous bile often fails to disperse throughout the abdomen.

Plain radiographs may reveal a focal or generalized loss of detail that is otherwise known as the *ground glass appearance*. A pneumoperitoneum (Figure 133-1) suggests perforation of a hollow viscous organ, penetrating trauma (including recent abdominal surgery) or, less commonly, the presence of gas-producing anaerobic bacteria. Intestinal tract obstruction or bowel plication should be ruled out. Prostatomegaly in male dogs and evidence of uterine distention in female dogs should be noted. Thoracic radiographs should be performed to rule out concurrent illness (infectious, neoplastic, or traumatic). The presence of bicavitary effusions increased the mortality rate of patients 3.3-fold compared with that of patients with peritoneal effusions alone.[11] Ultrasonography may be useful for defining the underlying etiology of peritonitis, in addition to its use in localizing and aiding retrieval of peritoneal effusion. In the case of a confirmed uroabdomen, preoperative contrast radiography (excretory urography or cystourethrography) is recommended to localize the site of urine leakage and aid in surgical planning. It should be noted that all patients should be hemodynamically and medically stabilized before diagnostic imaging is carried out.

133.5 TREATMENT

133.5.1 Medical Stabilization

The goals for animals with septic peritonitis are to identify and address the source of contamination in order to resolve the infection and treat the systemic consequences of such infection (i.e., fluid and electrolyte abnormalities and hypoperfusion). Before surgical intervention, a decision must be made whether additional hemodynamic and medical stabilization is indicated before proceeding, or whether this additional time and continued contamination of the abdominal cavity will result in further clinical decline that outweighs the benefits of further medical treatment.

The goals of medical treatment are to restore normal fluid and electrolyte balance and minimize ongoing contamination. Fluid resuscitation is initiated after obtaining pretherapy blood samples for a minimum database (packed cell volume, total solids, Azostix, dextrose), hematology, serum chemistry, and coagulation evaluation. Urine should be collected, if possible, for analysis with or without culture and sensitivity testing. Shock doses of crystalloids (90 ml/kg in the dog, 50 ml/kg in the cat) or a combination of isotonic crystalloids (20 to 40 ml/kg) and synthetic colloids (hydroxyethyl starch 10 to 20 ml/kg in the dog or 5 to 10 ml/kg in the cat; or 7% to 7.5% hypertonic saline in 6% dextran-70, 3 to 5 ml/kg IV over 5 to 15 minutes) should be administered to effect (see Chapter 65, Shock Fluids and Fluid Challenge). Because significant amounts of protein are lost into the peritoneal cavity, plasma and/or albumin administration may also be warranted. Electrolytes and glucose should be supplemented if indicated (see Chapters 55 and 69, Potassium Disorders and Hypoglycemia, respectively). After appropriate volume resuscitation, vasopressor therapy may be necessary to further alleviate hypotension. A urinary catheter may aid in diversion of infected urine in the case of a ruptured bladder or proximal urethra and allow for the necessary correction of any metabolic derangements (typically hyperkalemia and acidosis) (see Chapters 55 and 59, Potassium Disorders and Acid-Base Disturbances) before surgery.

Broad-spectrum antibiotic therapy should be initiated immediately after confirming the diagnosis of a septic peritonitis (see Chapters 108 and 109, Gram-Positive Infections and Gram-Negative Infections, respectively). *Escherichia coli, Clostridium* spp, and *Enterococcus* spp are common isolates. A second-generation cephalosporin such as cefoxitin (30 mg/kg IV q6-8h) may be used as a single agent or combination antibiotic therapy such as ampicillin or cefazolin (22 mg/kg IV q8h) administered concurrently with either enrofloxacin (10 to 20 mg/kg IV q24h [dog], 5 mg/kg q24h [cat]) or an aminoglycoside (amikacin 15 mg/kg IV q24h or gentamicin 6.6 mg/kg IV q24h). In the event that extended anaerobic coverage is necessary, metronidazole (10 mg/kg IV q12h) can be used. Aminoglycosides should be avoided unless renal insufficiency has been ruled out and the patient is well hydrated. It is advisable to tailor antibiotic therapy to the results of culture and sensitivity testing when they become available.

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133.5.2 Surgical Treatment

The goals of surgical treatment for septic peritonitis include resolving the cause of the infection, diminishing the infectious and foreign material load, and promoting patient recovery with enteral feeding, if indicated. A ventral midline celiotomy from xiphoid to pubis allows a thorough exploratory laparotomy to determine the underlying cause. Monofilament suture material is advocated in an animal with a septic process, and surgical gut is avoided because of its shortened half-life in this environment. Placement of nonabsorbable suture material or mesh within the abdominal cavity is not recommended in cases of septic peritonitis because either material may serve as a nidus for infection. If possible, the surgeon should isolate the offending organ from the rest of the abdomen with laparotomy sponges to prevent further contamination during correction of the problem.

Surgical treatment is tailored to the individual case and the underlying cause of the septic peritonitis. If a GI leakage is being treated, adjunctive procedures such as serosal patching or omental wrapping of the repaired site are recommended to reduce the incidence of postoperative intestinal leakage or dehiscence. Although heavily contaminated or necrotic omentum may necessitate partial omentectomy, preservation of as much omentum as possible is advised to promote drainage of the peritoneal cavity. In addition, surgical applications of the omentum relate to its immunogenic, angiogenic, and adhesive properties and include intracapsular prostatic omentalization for prostatic abscess formation,[12] pancreatic abscess omentalization,[13] omentalization of enterotomy or intestinal resection and anastomosis sites, and around gastrostomy or enterostomy tube sites. Because enteral nutrition directly nourishes enterocytes and decreases bacterial translocation across the intestinal wall, feeding tube placement (gastrostomy or jejunostomy) should be considered during initial surgical exploration.

After addressing the underlying cause to prevent further contamination of the peritoneum, the infectious and foreign material load must be diminished through a combination of debridement and lavage. Localized peritonitis should be treated with lavage of the affected area only, to minimize dissemination of the infection. A thorough lavage of the entire abdominal cavity with body-temperature sterile isotonic fluid is essential if peritonitis is generalized. The addition of antiseptics and antibiotics to lavage fluid is not beneficial and may actually be detrimental by inducing a superimposed chemical peritonitis. Lavage of the abdominal cavity is continued until the retrieved fluid is clear. All lavage fluid should be retrieved because fluid accumulation in the abdominal cavity impairs bacterial opsonization and clearance.[14]

If debridement and lavage can resolve gross foreign material or GI spillage and the source of contamination can be controlled, the abdomen should be closed primarily because potential complications are associated with open abdominal drainage and closed suction drains. All patients with abdominal drainage are susceptible to superinfection with nosocomial bacteria and are subject to massive fluid and protein losses.

Open peritoneal drainage is accomplished with a simple continuous pattern of nonabsorbable suture material in the rectus abdominus muscle, loosely enough to allow drainage through a gap of 1 to 6cm in the body wall (Color Plate 133-2). A preassembled, sterile bandage comprised of a nonadherent contact layer, laparotomy sponges or gauze pads, roll cotton or surgical towels, roll gauze, and an outer water-impermeable layer is placed to absorb fluid and protect the abdominal contents from the environment. Initially this bandage is replaced twice during the first 24 hours and daily thereafter, although the amount of drainage produced by an individual patient may dictate more frequent changes. A sterile-gloved finger may need to be inserted through the incision to break down adhesions and to allow thorough drainage of the peritoneal cavity. Alternatively, patients with severely contaminated tissues may be placed under general anesthesia and the abdomen explored and lavaged daily before reapplying the bandage. The quantity of fluid can be estimated by the difference in weight of the bandage before application and after removal. Abdominal closure typically can be performed 3 to 5 days following the initial surgery. The placement of a urinary catheter and collection system helps to limit contamination of the bandage and underlying exposed tissues.

Alternatively, the abdomen may be closed primarily and drainage accomplished with closed suction (Jackson-Pratt) drains.[15] Closed suction drainage has been advocated for treatment of generalized peritonitis because it has several advantages over open abdominal drainage, including a decreased risk of nosocomial infection, less intensive nursing care and bandaging requirements, decreased risk for evisceration, and the need for only one surgical procedure.[15] Disadvantages are that the drains may induce some fluid production and may become occluded, although in one study active drainage was maintained for up to 8 days with this technique in 30 dogs and 10 cats.[15] Additionally, closed suction drains allow daily quantitative and qualitative assessment of retrieved fluid for assessing the resolution of peritonitis. Typically, one drain placed between the liver and diaphragm is sufficient for small dogs and cats, and two drains are more appropriate for larger dogs (the fenestrated portion of second drain is placed in the caudal abdomen along the ventral body wall). The drain tubes exit the body wall through a paramedian stab incision and are sutured to the abdominal skin with a pursestring and Chinese finger-trap sutures (Color Plate 133-3).

After routine closure of the abdomen, the suction reservoir bulb is attached to the tubing with vacuum applied. A protective abdominal bandage is placed with sterile contact material around the tube-skin interface and is changed daily to allow assessment of this site. Fluid collected within the bulbs is emptied using aseptic technique, and the volume is recorded every 4 to 6 hours, or more frequently if needed. Drains are removed by applying gentle traction at a time when the volume of fluid production has decreased significantly and cytologic analysis suggests resolution of the peritonitis (decreasing numbers of nondegenerative neutrophils in the absence of bacteria). A sterile bandage is again reapplied to cover the drain exit site until the following day.

133.5.3 Postoperative Care

Postoperative care for patients with peritonitis is typically intense because these patients are critically ill and subject to a variety of complications.[7] Aggressive fluid therapy is a necessity, particularly in patients with continued fluid losses from abdominal drainage. Electrolytes and acid-base status should be assessed routinely during the postoperative period and corrected as needed. Because anemia and hypoproteinemia are common complications in these patients, blood component therapy and synthetic colloidal support are often necessary, with a goal of maintaining a packed cell volume greater than 24%, serum protein over 3.5 g/dl, and colloid osmotic pressure higher than 15 mm Hg.

Proper nutrition will provide a source of protein that is greatly needed in these patients. Failing to meet nutritional demands, either with parenteral or enteral nutrition, may contribute to impaired wound healing and immune defenses. Enteral feeding is preferred over parenteral feeding but may be stymied by the anorectic patient unless GI feeding tubes were placed during the original surgery. If this was not done, nasoesophageal tubes can be placed in patients unable to tolerate more anesthesia or esophagostomy tubes in those that can. Animals with refractory vomiting typically require parenteral nutrition.

Postoperative hypotension may be treated with vasopressor therapy, but only after addressing any underlying hypovolemia (see Chapter 176, Vasoactive Catecholamines). Proper analgesia is required to ensure patient comfort and to diminish the negative cardiovascular effects associated with overactive sympathetic stimulation (see Chapter 164, Analgesia and Constant Rate Infusions). Other complications, including cardiac arrhythmias, disseminated intravascular coagulation, and systemic inflammatory response syndrome can be found in other chapters (see Chapters 11 and 107, Systemic Inflammatory Response Syndrome and Septic Shock, respectively).

133.6 PROGNOSIS

The prognosis for animals with peritonitis depends on the underlying etiology and whether or not infection is present. Studies in which patients have benefited from advances in critical care management cite overall survival rates of 50% to 70%.[1,4,16] Cats were reported to have a lower survival rate than dogs in two studies[1,16]; however, another study focusing on 51 cats with septic peritonitis found a 70% survival in animals in which treatment was pursued.[5] Poor prognostic indicators for animals with septic peritonitis have included refractory hypotension, cardiovascular collapse, disseminated intravascular coagulation, and respiratory disease.[15,16] Mortality rates in patients with septic peritonitis secondary to GI leakage have been reported to vary between 30% and 85%.[1,2,4,18,19] Bacterial contamination was highly associated with mortality in animals with bile peritonitis in one study, and only 27% (3 of 11) of animals with septic biliary effusion survived compared with 100% (6 of 6) with aseptic effusions.[20] Cats with uroperitoneum have an overall survival rate or 62%,[21] whereas the survival rate in dogs is slightly lower at 43% to 56.2%.[22] Survival rates appear to be similar in patients with septic peritonitis treated with primary closure, open peritoneal drainage, or closed suction drainage.[16,17]

133.7 SUGGESTED FURTHER READING*

MF Costello, KJ Drobatz, LR Aronson, LG King: Underlying cause, pathophysiologic abnormalities, and response to treatment in cats with septic peritonitis: 51 cases (1990-2001). *J Am Vet Med Assoc*. **225**, 2004, 897, Clinical presentation, treatment, and outcome of 51 cats with septic peritonitis studied to provide useful information regarding underlying cause, pathophysiologic abnormalities, and response to treatment in this species. This is the first focused examination of this condition in cats; previous studies had focused on dogs or a combined population of dogs and cats.

KL Evans, DD Smeak, DS Biller: Gastrointestinal linear foreign bodies in 32 dogs: a retrospective evaluation and feline comparison. *J Am Anim Hosp Assoc*. **30**, 1994, 445, Retrospective study evaluating case records of 32 dogs with gastrointestinal linear foreign bodies treated surgically to assess clinical signs, laboratory abnormalities, radiographic signs, surgical procedures, and complications. Peritonitis evident in 41% of cases, increasing the probability of death (both found to occur at nearly twice the rate previously described for feline patients with this condition).

BDX Lascelles, AT Blikslager, SM Fox, D Reece: Gastrointestinal tract perforation in dogs treated with a selective cyclooxygenase-2 inhibitor: 29 cases (2002-2003). *J Am Vet Med Assoc*. **227**, 2005, 1112, A retrospective study examining risk factors associated with gastrointestinal tract perforation in 29 dogs treated with a selective cyclooxygenase-2 inhibitor. Perforation attributable to a multitude of factors, prompting the authors to warn against using this type of medication outside of the recommended dosage and to avoid its use in close temporal association with other less-selective nonsteroidal antiinflammatory medications or steroids.

* See the CD-ROM for a complete list of references

134 Chapter 134 Gastric Dilatation-Volvulus and Bloat

Susan W. Volk, VMD, PhD, DACVS

134.1 KEY POINTS

- Gastric dilatation-volvulus (GDV) is a life-threatening condition that requires aggressive emergency medical stabilization, surgical intervention, and intensive postoperative care to optimize management.
- The pathogenesis of GDV is complex, with both genetic and environmental influences.
- Distention and displacement of the stomach cause cardio-respiratory dysfunction and gastrointestinal compromise. A cascade of pathophysiologic events further impairs these systems as well as the metabolic, hemolymphatic, renal, and central nervous systems.
- Potential life-threatening postoperative complications include cardiac arrhythmias, persistent hypotension, disseminated intravascular coagulation, peritonitis, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome.
- Client education is key and promotes early intervention and decreased incidence of this condition through breeding and home treatment practices.
- Despite often challenging case management, the overall survival rate for patients treated appropriately for GDV approaches 85%.

134.2 INTRODUCTION

Acute gastric dilatation with or without volvulus is a life-threatening condition that is classically described in large or giant breed dogs with deep chests, and appears to occur more frequently in older animals. Although there has been much debate whether dilatation or volvulus occurs first in the gastric dilatation-volvulus (GDV) syndrome, it is plausible that either may occur primarily as isolated cases of both conditions occur. Regardless of the sequence of events, once gastric distention and malpositioning occur, the compression of low-pressure (venous) intraabdominal vasculature leads to cardiovascular, respiratory, and gastrointestinal (GI) compromise. Impaired perfusion causes secondary compromise of multiple organs, the hemolymphatic system, and the metabolic system. Elements of individual treatment regimens remain controversial; however, treatment strategies shown to yield the most successful outcomes combine aggressive emergency medical diagnostics and therapeutics with early surgical intervention and intensive postoperative critical care management. It is clear that an understanding of the etiology, pathophysiology, and clinical features of this syndrome contribute to improved survival rates.

134.3 PATHOGENESIS

When considering etiology, it is important to realize that several subpopulations of dogs have gastric dilatation. As previously stated, this may occur in the presence or absence of volvulus and, less commonly, volvulus may occur without significant dilatation. Rapid, significant gastric distention with gas and the ensuing cardiorespiratory dysfunction lead to the typical acute clinical picture, although some dogs may have chronic, subtle GI dysfunction. Multiple contributing factors have been identified and influence incidence within a genetically susceptible population.

Although small dogs and cats can develop GDV, it is predominantly a syndrome of the large and giant breed dogs. Certain breeds, including the Great Dane, Weimaraner, Saint Bernard, Gordon Setter, Irish Setter, and Standard Poodle, are at significantly increased risk.[1] Furthermore, having a first-degree relative with a history of GDV was found to be a significant risk factor.[2] It has been hypothesized that genetic predisposition to GDV may occur through inheritance of conformation, personality, or temperament that predisposes to the condition. Anatomic studies have shown a correlation between increased thoracic depth-to-width ratio and incidence of GDV within certain breeds.[3,4] It has been speculated that this conformation may inhibit eructation. Failure of normal eructation and pyloric outflow mechanisms may be a prerequisite for gastric dilatation.[5] Stretching of gastric ligaments, as may occur with previous dilatation, large intraabdominal masses, or splenic torsion may facilitate development of the condition.[6,7]

Overeating, postprandial exercise, and food type have all been incriminated as causes of GDV, but there remains a lack of evidence to support these assumptions. Based on the results by Glickman and colleagues[2] examining nondietary risk factors for GDV in 1637 large and giant breed dogs, feeding fewer meals per day or several small meals per day, moistening dry food before feeding, and restricting exercise or water intake immediately before or after eating were not associated with a decreased risk of GDV on multivariate analysis. In this large, prospective study, factors significantly associated with increased risk were increasing age, having a first-degree relative with a history of GDV, eating faster (for large but not giant breeds of dogs), and having a raised feeding bowl.

A separate study documented that an episode of stress (e.g., boarding, traveling, a veterinary visit) occurred more frequently during the period immediately before development of a GDV than in a comparable disease-free population.[8] The propensity to be influenced by a stressful event may be related to the personality of a given individual. In a prospective cohort study of 1914 dogs, the only breed-specific characteristic significantly associated with GDV was a negative correlation between owner-perceived happiness and incidence of GDV.[9] However, other studies have suggested that fearful or aggressive dogs may be at increased risk for developing GDV.[2,8] The findings in these studies and others may help decrease the incidence of GDV by providing owners and breeders with guidelines for breeding and treatment practices.

134.4 PATHOPHYSIOLOGY

Gastric distention and displacement directly affect the cardiovascular, respiratory, and GI systems. Secondary effects on these and other systems (i.e., metabolic, hemolymphatic, renal, and central nervous systems) ensue. Shock is the life-threatening abnormality in dogs with GDV, and an understanding of the cause of this state allows rational treatment. Severe gastric distention results in compression of the intraabdominal veins (caudal vena cava, portal vein, and splanchnic vasculature). This venous occlusion results in decreased venous return and increased venous pressure (splanchnic pooling and portal hypertension). The combination diminishes cardiac output and systemic blood pressure. The collateral circulation is unable to handle the venous return, leading to interstitial edema and loss of intravascular volume, which further contribute to poor perfusion of major organs.

In addition, gastric distention prevents caudal displacement of the diaphragm and therefore impedes normal respiratory excursion. To compensate, respiratory rate and effort may increase. These efforts may become inadequate and eventually respiratory acidosis, due to impaired carbon dioxide clearance, might contribute further to the metabolic acidosis that exists secondary to poor tissue perfusion (lactic acidosis). Aspiration pneumonia may further exacerbate this respiratory compromise.

The increased intraluminal gastric pressures impair flow through the gastric wall vasculature and this, combined with poor cardiac output, may lead to gastric necrosis. Avulsion, thrombosis, and stretching of the short gastric arteries are common and may further contribute to diminished perfusion of the stomach. Mucosal hemorrhage and necrosis are common. Susceptibility of the mucosa to damage by hypoperfusion may be exacerbated by the acidic environment of the gastric lumen and high metabolic demands. Decreased gastric perfusion results in serosal hemorrhage and edema of the stomach wall, which begins in the fundus and spreads to the body of the stomach. Bacterial translocation from the stomach or other portions of the poorly perfused intestinal tract may lead to septicemia. Severe compromise to the gastric wall results in necrosis and perforation, with resultant peritonitis.

Cardiac arrhythmias, mainly ventricular in origin, occur in approximately 40% of patients with GDV.[10,11] Several factors have been implicated in the cause of cardiac arrhythmias. Coronary blood flow in experimentally induced GDV is decreased by 50%.[12] Histologic lesions compatible with myocardial ischemia are seen in both experimental and spontaneous GDV and may establish ectopic foci of electrical activity. Circulating cardiostimulatory substances such as epinephrine and cardioinhibitory substances such as myocardial depressant factor have also been implicated in the generation of arrhythmias.

Acid-base and electrolyte imbalances are not seen consistently in dogs with GDV. Cellular hypoxia caused by systemic hypoperfusion may result in an increased production of lactic acid by anaerobic energy production, resulting in a metabolic acidosis. Blood pH may be normalized by a concurrent metabolic alkalosis caused by sequestration of hydrogen and chloride ions in the stomach lumen (causing a mixed acid-base disorder). Several pathophysiologic events may promote the development of hypokalemia, including the administration of a large volume of low-potassium fluids, sequestration of potassium within the stomach or loss through vomiting or lavage, hyperchloremic metabolic alkalosis with transcellular shifting, activation of renin-angiotensin-aldosterone system, and catecholamine-induced shifting of potassium into cells. Blood glucose levels may also fall in the later stages of shock as energy demands cannot be met by the inefficient production of adenosine triphosphate through anaerobic metabolism.

Infarction of splenic arteries and thrombosis of splenic veins may occur, resulting in splenic necrosis. Disseminated intravascular coagulation (DIC) is seen frequently in dogs with GDV.[13] Contributing factors include pooling of blood in the caudal vena cava, portal vein, or splanchnic circulation, tissue hypoxia, acidosis, endotoxemia, and sepsis.

134.5 HISTORY AND CLINICAL SIGNS

Affected dogs are often adult large, deep-chested breeds, although GDV in small breed dogs and puppies as young as 1 month has been reported. Typically, the onset of clinical signs is acute, with affected dogs appearing restless, uncomfortable, and anxious. Most affected dogs salivate and may retch or attempt to vomit. The owners may note the distended abdomen, although this may be difficult to appreciate in deep-chested, well-muscled, or obese individuals.

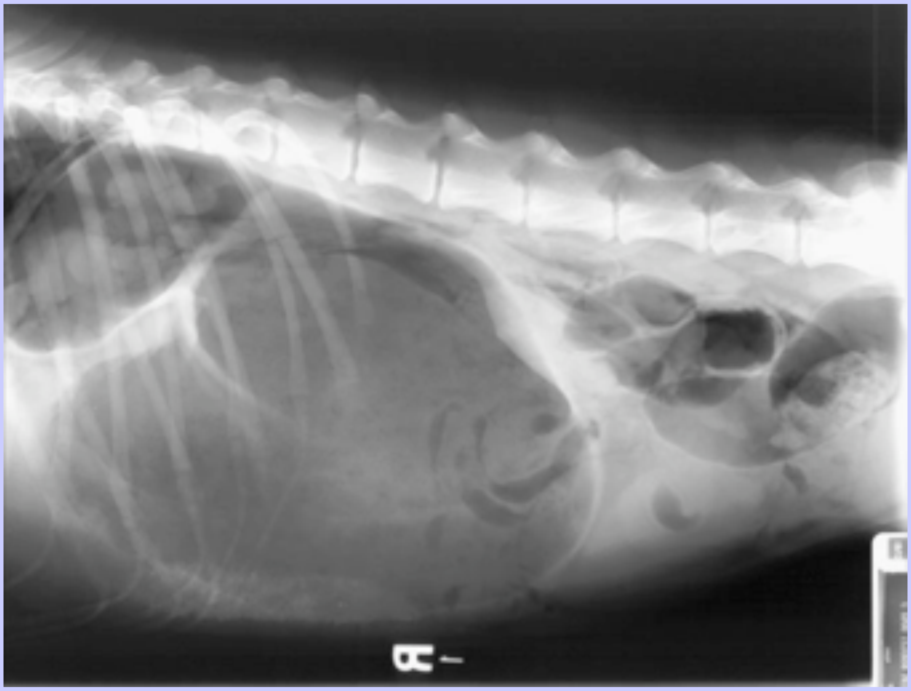
134.6 PHYSICAL EXAMINATION

Physical examination parameters are manifestations of the circulatory and respiratory compromise that results from acute gastric distention and displacement. Dogs often present in cardiovascular shock, with depressed mentation, pale mucous membranes, prolonged capillary refill time, cool extremities, and rapid, weak pulses. Irregular cardiac rhythms and pulse deficits may be present. Tachypnea or dyspnea, or both, may reflect both discomfort and a reduction in tidal volume due to gastric distention. The abdomen can vary from unremarkable on palpation, through distended and firm, to tympanic. Splenic congestion may lead to the finding of splenomegaly. If presentation has been delayed, dogs can be collapsed and comatose.

134.7 DIAGNOSIS

Complete blood count may reveal evidence of hemoconcentration and a stress leukogram. Platelet consumption and/or loss may lead to thrombocytopenia. The presence of three or more abnormal hemostatic parameters (prolonged prothrombin or activated partial thromboplastin time, hypofibrinogenemia, thrombocytopenia, elevated fibrin degradation products concentration, and antithrombin III depletion) correlates with gastric necrosis.[13] 585
Hepatocellular damage and biliary stasis may be evidenced by elevations in alanine transaminase and total bilirubin 586
levels, respectively. Cardiovascular and renal compromise and hypovolemia may lead to elevations in blood urea nitrogen and creatinine. Potassium may be elevated, normal, or low but is typically low for the reasons stated above. Plasma lactate concentration is an established predictor of gastric necrosis and survival in dogs with GDV.[14]

Figure 134-1 The right lateral recumbent view is the radiographic view of choice for diagnosis of gastric dilatation-volvulus. In this view, the pylorus moves to a cranial position in a dog with gastric dilatation-volvulus and is separated by a soft tissue opacity from the body of the stomach. In addition, in this example, enlargement of the spleen is evident and the serosal surfaces of the stomach, small intestine, and diaphragm are well defined, indicating a pneumoperitoneum.



Abdominal radiography is used to differentiate simple gastric dilatation from dilatation with volvulus and to rule out other conditions. All dogs should be stabilized medically before radiographs are taken. The right lateral recumbent view is the view of choice.[15] If possible, a dorsoventral view may also be taken to help delineate gastric position. Ventrodorsal positioning may lead to further cardiovascular compromise and may predispose to aspiration pneumonia should the patient regurgitate or vomit. The pylorus in a dog with GDV moves cranial to and is separated by a soft-tissue opacity from the body of the stomach (called *reverse C, double bubble,* or *Popeye sign*) in the lateral projection and to the left of midline on the dorsoventral view (Figure 134-1). In comparison, the pylorus lies ventral to the fundus and to the right of midline in a dog without volvulus. Although gastric pneumatosis (intramural gas) and pneumoperitoneum suggest gastric necrosis and possibly perforation, it is important to remember that gastric air may be introduced when a trocar is used in the emergency stabilization of the patient before radiographs are taken.[16] Chest radiographs may also be indicated in older animals that might have coexisting disease, animals with hypoxemia, or patients suspected of having concurrent cardiac disease.

134.8 TREATMENT GOALS

The most important goal of treatment is correction of circulatory shock. Aggressive preoperative correction of cardiovascular collapse before surgery has dramatically improved patient survival to an overall rate of approximately 85%.[10,11,14] Following initial stabilization, treatment goals include decompression of the stomach, differentiation of dilatation versus dilatation-volvulus, repositioning and pexying the stomach if volvulus exists, and early diagnosis and treatment of complications. Fluid resuscitation is initiated after placement of at least two large-bore (14 to 18 gauge) catheters in the cephalic or jugular veins. Blood samples can be obtained at this time for a minimum database (packed cell volume, total solids, Azostix, and dextrose), hematology, serum chemistry, and coagulation evaluation. Shock doses of crystalloid fluids (90 ml/kg) or a combination of isotonic crystalloids (20 to 40 ml/kg) and synthetic colloids (hydroxyethyl starch 10 to 20 ml/kg; or 7% hypertonic saline in 6% dextran-70 5 ml/kg IV over 5 to 15 minutes) should be administered to effect (see Chapter 65, Shock Fluids and Fluid Challenge). After appropriate volume resuscitation, vasopressor therapy may be necessary to further alleviate hypotension. During the initial examination and resuscitation, supplemental oxygen should be administered, if possible, to optimize oxygen saturation of hemoglobin. If available, continuous electrocardiographic (ECG) monitoring should be performed and arrhythmias (typically ventricular) treated if they interfere with cardiac function and output. Broad-spectrum antibiotic therapy should be considered because these animals are at high risk for bacterial translocation from the GI tract to the bloodstream.

Gastric decompression should be attempted only after cardiovascular resuscitation has begun. Decompression will further improve cardiorespiratory function; however, additional cardiovascular insult occurs with the rapid release of endotoxins and ischemic by-products (reperfusion injury). Gastric decompression usually can be accomplished with orogastric intubation (Color Plate 134-1). Sedation may be required and can be accomplished using a combination of oxymorphone (0.1 mg/kg IV), buprenorphine (0.01 mg/kg IV) or butorphanol (0.2 to 0.4 mg/kg), and diazepam (0.2 to 0.25 mg/kg IV). Intubation may be desirable to protect the airway and prevent aspiration pneumonia. The smooth-surfaced orogastric tube should be marked to a length of the distance from the nares to the caudal edge of the last rib and the lubricated tube not passed beyond this point. In the event that the orogastric tube cannot be passed easily, trocar insertion should be performed using a large-gauge, short needle or over-the-needle catheter in a region of the left or right cranial, dorsolateral abdomen. This should be performed in an area that exhibits the greatest tympany and that has been clipped and aseptically prepared.

Continued periodic assessment of physical parameters (heart rate, peripheral pulse pressure and quality, mucous membrane color, capillary refill time, and gastric distention) as well as laboratory data (packed cell volume, total solids, acid-base status, and electrolyte values) should be performed to ensure treatment remains tailored to the individual's response to therapy. As stated previously, only after cardiovascular stability is achieved should radiographs be attempted. Immediate surgical intervention is indicated for animals with GDV.

Dogs with gastric dilatation in the absence of volvulus (GD) typically do not require immediate surgical intervention, although gastropexy is recommended for these patients to help prevent the development of GDV in the future. Conservative treatment in these patients is tailored to the individual patient and may consist of intravenous fluid therapy as described above and orogastric intubation as needed. In addition, simethicone (2 to 4 mg/kg PO q6h) and metaclopramide (0.2 to 0.4 mg/kg SC q8h) may be considered in order to decrease the amount of gas and promote gastric emptying, respectively. It should be noted that even in the absence of radiographic evidence of gastric volvulus, surgical exploration should be recommended for GD patients who are unresponsive to medical treatment (repeated bloating, persistent hypotension, and/or tachycardia).

134.9 SURGICAL TREATMENT

The goals for surgery are to decompress and reposition the stomach, assess viability of the stomach and spleen, remove irreversibly compromised tissue, and create a permanent adhesion between the stomach and body wall to help prevent recurrence of gastric volvulus. A large ventral midline incision is made, taking care not to damage abdominal viscera pushed up to the linea by gastric distention. Typically, the pylorus has moved from its normal position next to the right body wall toward the left body wall, in a clockwise direction. The rotation may be 90 to 360 degrees but most commonly is 180 to 270 degrees. With this type of rotation, the greater omentum is found draped over the cranial abdominal organs.

The stomach is decompressed by orogastric intubation (by the anesthetist with guidance by the surgeon) or via gastrocentesis and is rotated back into its normal position. The pylorus can be located by tracing the duodenum (identifiable by the attached pancreas) forward from the duodenocolic ligament. By gently bringing the pylorus back to the right of midline using one hand and using the other hand to push the body of the stomach dorsally, the stomach is derotated. An orogastric tube may be used to completely decompress the stomach and empty ingesta. Gastrotomy is not recommended for the removal of suspected food particles but is warranted if potentially obstructive material is present within the gastric lumen.

Next, the stomach and the spleen should be assessed for viability and gastric resection or splenectomy performed as needed. The spleen should be removed only if it has thrombosed or been damaged by the gastric volvulus; it is rarely twisted otherwise. Partial gastrectomy is required when gastric necrosis has occurred, usually along the greater curvature. Gastric viability is assessed by examination of serosal color, palpation of gastric wall thickness, and preservation of arterial bleeding if incised. Gray or black coloration and palpable thinning of the stomach are signs of necrosis. Serosal coloration within areas of viable tissue may improve dramatically within minutes of decompression and repositioning. Gastric resection may be accomplished by preplacing stay sutures to minimize or prevent additional abdominal contamination, followed by resection to bleeding tissue and closure.

Whether hand-sewing or stapling (TA-90 or GIA-50) is used for closure, a second inverting suture line is recommended.[17] Invagination of necrotic tissue has also been used to treat gastric necrosis. Because this technique does not require opening of the gastric lumen, it is technically less demanding and is theoretically less likely to result in peritoneal contamination through gross spillage during partial gastrectomy or due to suture dehiscence; however, it should be noted that invaginated tissue may be prone to ulcer formation.[18,19] Although there are risks associated with gastric resection and invagination, the devastating sequelae of perforation and peritonitis resulting from necrotic tissue that is not excised make it advisable to remove or invaginate any gastric tissue of questionable viability. Gastric necrosis has been associated with the development of several life-threatening complications including peritonitis, disseminated intravascular coagulation, sepsis, and arrhythmias.[20] Although two large retrospective studies examining postoperative outcome in dogs surgically treated for GDV (295 and 166 cases) did not agree whether gastric resection was a risk factor for death, these studies both suggest that with aggressive preoperative and postoperative management, 70% to 74% of dogs with gastric resections may survive to discharge.[10,14,20]

Many procedures have been described to pexy the pyloric antral region of the stomach to the right body wall. These include the tube, incisional, muscular flap, circumcostal, and belt loop gastropexies, as well as various modifications of the above. The aim is to create a permanent adhesion between the antral region of the stomach and the right body wall. An incisional gastropexy is accomplished easily and quickly by making an incision about 5 cm long in the transverse abdominus muscle just caudal to the last rib, and a corresponding incision is made in the seromuscular layer (taking care not to enter the gastric lumen). The orientation of the incisions reflects an attempt to preserve a relatively normal gastric position when the two edges of each incision are sutured together using either polypropylene or polydioxanone. The pexy site should not be incorporated into the abdominal closure because the stomach could be damaged if cranial abdominal surgery is required at a future date.

Although there is some variability in strength of the adhesions formed using the various techniques when tested in vitro, recurrence rates are similar for all the above techniques when performed properly (percutaneous endoscopic gastrostomy tubes are not recommended because of inconsistent adhesion formation).[21] The tube gastropexy may be associated with a higher morbidity because of premature tube removal and peristomal cellulitis; however, it may be useful for continued gastric decompression of air and gastric secretions and for administration of medications and nutritional support to anorexic patients postoperatively.

The surgical technique used is probably less important than the surgeon's familiarity with one of the established techniques and the surgeon's ability to perform it proficiently and efficiently.

134.10 POSTOPERATIVE CARE

The aim of postoperative management is to maintain tissue perfusion. Because of substantial fluid loss into the peritoneal cavity and GI tract, reasonably high fluid rates often are required for the first 48 to 72 hours. Mucous membrane color, capillary refill time, packed cell volume, total solid values, urine output, ECG, blood pressure, and acid-base balance should be monitored closely postoperatively. Dogs recovering well from surgery can be offered water first, and then a small amount of food if water is tolerated on the first or second day after surgery. These dogs can be weaned gradually off their intravenous fluids over 2 days. Because of the high incidence of gastric mucosal compromise, nonsteroidal antiinflammatory drugs are avoided, and histamine-2 receptor 587 antagonists (ranitidine, cimetidine, famotidine) and coating agents (sucralfate) should be considered. 588

Cardiac arrhythmias often begin 12 to 24 hours after surgery. Continuous ECG monitoring is ideal. Contributing factors include poor myocardial perfusion, electrolyte disturbances, acidosis, DIC, pain, and myocardial depressant factor. If arrhythmias occur, these contributing factors should be sought and treated. Antiarrhythmic therapy should be considered if cardiac function is impaired (poor pulse quality or pulse deficits) or if serious electrical changes are evident (such as R on T phenomenon, multiform ventricular premature contractions, or when sustained ventricular tachycardia occurs with a heart rate of >180 beats/min), because this rate probably impairs ventricular filling and therefore cardiac output) (see Chapters 46 and 47, Supraventricular Tachyarrhythmias and Ventricular Tachyarrhythmias, respectively). Reports have been conflicting as to whether the presence of arrhythmias negatively affects the prognosis.[10,11,20]

Perioperative risk factors significantly associated with death before suture removal include hypotension at any time during hospitalization, combined splenectomy and partial gastrectomy, peritonitis, sepsis, and DIC.[20] Contributing factors for the development of DIC include pooling of blood in portal circulation and caudal vena cava, sepsis, vascular thrombosis, endotoxemia, acidosis, tissue hypoxia, and splenic congestion. This condition may persist into the postoperative period and require appropriate treatment with fluids, plasma, and heparin (see Chapter 117, Hypercoagulable States). Sepsis can occur during the postoperative period. Gastric leakage must be ruled out; however, it is important to consider other culprits in these patients such as aspiration pneumonia. The underlying cause should be identified and will help guide therapy. Systemic inflammatory response syndrome and multiple organ dysfunction syndrome may occur in critically ill patients postoperatively (see Chapter 11, Systemic Inflammatory Response Syndrome).

134.11 OWNER RECOMMENDATIONS

Based on available information, veterinarians should discuss preventive strategies with owners of large and giant breed dogs. These would include not feeding dogs from a raised food bowl and trying to ensure that large breed dogs eat more slowly (although this may be contraindicated in giant breed dogs). This may involve supervising feedings and separating dogs in households with multiple pets to decrease competition at feeding time. On the basis of the findings of Glickman and colleagues[2], one of the strongest recommendations to prevent GDV is to remove from the breeding pools dogs that have a first-degree relative that has had a GDV. Prophylactic gastropexy, either laparoscopically or via a conventional approach, has been shown to reduce the lifetime probability of death due to GDV in at-risk breeds and should therefore be offered to owners of these dogs.[22-24]

134.12 SUGGESTED FURTHER READING*

DJ Brockman, DE Holt, RJ Washabau: Pathogenesis of acute canine gastric dilatation-volvulus syndrome: is there a unifying hypothesis?. *Compendium*. **22**, 2000, 1108, *An excellent review of risk factors for GDV, proposing a unifying hypothesis to explain the pathogenesis.*

LT Glickman, NW Glickman, DB Schellenberg, et al.: Multiple risk factors for the gastric dilatation-volvulus syndrome in dogs: a practitioner/owner case-control study. *J Am Assoc Hosp Assoc*. **33**, 1997, 197, *A retrospective risk factor analysis that determined extrinsic and intrinsic risk factors for the development of GDV in 101 dogs compared with their breed-matched, size-matched, and age-matched controls.*

C Hedlund, TW Fossum: Surgery of the digestive system. In TW Fossum (Ed.): *Small animal surgery*. 2007, Mosby, St Louis, *Easy to follow, user-friendly surgical textbook that provides clear descriptions and helpful diagrams of the most commonly used gastropexy techniques, partial gastrectomy, and splenectomy*.

* See the CD-ROM for a complete list of references

135 Chapter 135 Acute Renal Failure

Catherine E. Langston, DVM, DACVIM

135.1 KEY POINTS

- Therapeutic intervention during the initiation stage of acute renal failure (ARF) is more likely to be successful than treatment during the extension, maintenance, or recovery phases.
- Prerenal failure is rapidly reversed, whereas animals with intrinsic parenchymal failure may take weeks to months to recover. Long-standing prerenal ischemia can lead to intrinsic renal failure.
- Careful attention to fluid balance, with accurate monitoring of urine output, fluid administration guided by intake and output, and frequent reassessment of the patient, is an important feature of treatment.
- Anuric and oliguric ARF carry a worse prognosis than does polyuric ARF.
- Polyuric ARF can be associated with extreme fluid losses from high urine output.
- Mortality rates for ARF are high (≈60%).

135.2 INTRODUCTION

Acute renal failure (ARF) is an abrupt decline in filtration and excretory function of the kidney, leading to retention of uremic toxins and dysregulation of fluid, electrolyte, and acid-base balance. Although anuria and oliguria are classic features of ARF, nonoliguric and polyuric ARF are common and carry a better prognosis.

135.3 ETIOLOGY

ARF can be categorized into prerenal, intrinsic renal parenchymal, and postrenal causes. Prerenal causes include decreases in renal blood flow or perfusion or excessive vasoconstriction. Prerenal azotemia rapidly reverses when the inciting cause is eliminated. Intrinsic renal parenchymal causes include prolonged hemodynamic or ischemic events (extension of prerenal causes), infectious diseases, toxins, or systemic diseases with renal manifestations. Box 135-1 lists substances with a nephrotoxic potential. Postrenal failure is due to obstruction or diversion of urine flow, including urethral obstruction, bilateral ureteral obstruction or unilateral obstruction with a nonfunctional contralateral kidney, or urine leakage. Restoration of urine flow rapidly resolves azotemia, although prolonged obstruction may lead to intrinsic parenchymal renal failure. Calcium oxalate nephroliths and ureteroliths are encountered in cats with increasing frequency. This condition commonly has many features of ARF, although there is frequently a significant component of chronic renal damage.[1]

135.4 PATHOPHYSIOLOGY

ARF proceeds through four phases. The initiation phase is the period of renal injury. Intervention at this phase may prevent progression to more severe injury, but changes in glomerular filtration rate (GFR) and urine specific gravity are not apparent at this stage. During the extension phase, cellular injury progresses to cell death. The maintenance phase occurs when irreversible renal damage has occurred. Removal of the initiating cause at this stage does not alter the existing damage. The recovery phase may last weeks to months.[2]

135.5 CLINICAL PRESENTATION

135.5.1 History

Listlessness, vomiting, diarrhea, and anorexia are common historical findings.[3] Oliguria, anuria, or polyuria may be reported. Compensatory polydipsia may be present or may be overshadowed by anorexia. Less common historical findings include seizures, syncope, ataxia, and dyspnea.

135.5.2 Physical Examination

Dehydration is common. Other findings include uremic halitosis, oral ulceration, tongue tip necrosis, scleral injection, tachycardia or bradycardia, hypothermia, and cutaneous bruising. A hallmark of ARF is enlarged, painful kidneys. Melena or diarrhea may be present from uremic gastritis or enteritis. Signs of the primary ailment causing renal failure (e.g., disseminated DIC intravascular coagulation, vasculitis) may predominate.

135.6 DIAGNOSIS

135.6.1 Laboratory Tests

The urine specific gravity will be isosthenuric (1.007 to 1.015). With acute tubular necrosis (most of ARF), a urine dipstick may reveal glucosuria (without hyperglycemia), proteinuria, and microscopic hematuria. The urine pH is usually acidic, unless there is a concurrent bacterial urinary tract infection. Urine sediment examination may show white blood cells, red blood cells, and granular casts. Calcium oxalate crystals in large numbers are indicative of ethylene glycol intoxication, although a few oxalate crystals may be present normally. Urine culture is important to document pyelonephritis and guide antimicrobial therapy.

Hematocrit may be elevated from hemoconcentration or decreased from gastrointestinal (GI) blood loss. Platelet count may be normal or low, although uremia induces a thrombocytopathy, prolonging the buccal mucosal bleeding time despite a normal coagulation profile.

The severity of azotemia depends on disease and duration. The ratio of blood urea nitrogen to creatinine can be high from GI bleeding or dehydration, or it can below in early stages of ARF. Ionized calcium levels tend to be normal, but acute severe hyperphosphatemia can decrease total calcium as a result of the law of mass action. Ethylene glycol, however, may cause a profound ionized hypocalcemia, due to both severe hyperphosphatemia and chelation of calcium by oxalate. Anion gap is high because of retained organic and inorganic acids that the damaged kidney is unable to excrete. The anion gap is calculated by the formula: 590 591

135.6.1.1 Box 135-1 Substances With Nephrotoxic Potential[2]

135.6.1.1.1 Therapeutic Agents

135.6.1.1.1.1 Antimicrobial Agents

- Aminoglycosides
- Penicillins
- Nafcillin
- Cephalosporins
- Sulfonamides
- Fluoroquinolones
- Carbapenems
- Aztreonam
- Rifampin
- Tetracyclines
- Vancomycin

135.6.1.1.1.2 Antifungal Agents

- Amphotericin B

135.6.1.1.1.3 Cancer Chemotherapy

- Cisplatin and carboplatin
- Methotrexate

Doxorubicin

Azathioprine

Adriamycin

135.6.1.1.1.4 Antiviral Agents

Acyclovir

Foscarnet

135.6.1.1.1.5 Antiprotozoal Agents

Pentamidine

Thiacetarsamide

Trimethoprim-sulfamethoxazole

Sulfadiazine

Dapsone

135.6.1.1.1.6 Miscellaneous

Allopurinol

Cimetidine

Apomorphine

Deferoxamine

Streptokinase

Dextran-40

Methoxyflurane

Penicillamine

Acetaminophen

Tricyclic antidepressants

e-Aminocaproic acid

Lipid-lowering agents

Nonsteroidal antiinflammatory drugs

Diuretics

Angiotensin-enzyme converting inhibitors

135.6.1.1.1.7 Immunosuppressive Drugs

Cyclosporine

FK-506

Interleukin-2

135.6.1.1.2 Nontherapeutic Agents

135.6.1.1.2.1 Heavy Metals

Mercury

Uranium

Lead

Bismuth salts

Chromium

Arsenic

Gold

Cadmium

Thallium

Copper

Silver

Nickel

Antimony

135.6.1.1.2.2 Endogenous

Hemoglobin

Myoglobin

135.6.1.1.2.3 Organic Compounds

Ethylene glycol

Carbon tetrachloride

Chloroform

Pesticides

Herbicides

Solvents

135.6.1.1.2.4 Miscellaneous Agents

- Gallium nitrate
- Diphosphonate
- Mushrooms
- Grapes or raisins
- Calcium antagonists
- Snake venom
- Bee venom
- Lily
- Illicit drugs
- Radiocontrast agents

$$\text{Anion gap} = (\text{Na}^{+} + \text{K}^{+}) - (\text{HCO}_3^{-} + \text{Cl}^{-})$$

where Na^{+} = sodium, K^{+} = potassium, HCO_3^{-} = bicarbonate, and Cl^{-} = chloride. Normal anion gap is 10 to 15 mEq/L.

135.6.2 Imaging

Survey abdominal radiographs may show normal kidneys or renomegaly with normal shape. Nephroliths or ureteroliths may be readily apparent, although obstructing ureteroliths may be below the limit of resolution. Abdominal ultrasonography usually shows normal or enlarged kidneys with normal architecture. Bilateral pyelonephritis or obstruction characterized by renal pelvic dilation, or lymphosarcoma characterized by a diffusely thickened cortex, could cause ARF. With ethylene glycol intoxication, oxalate crystal deposition in the kidneys increases the echogenicity, making the kidneys hyperechoic, or “bright.” An intravenous pyelogram can aid in the identification of pelvic, ureteral, and cystic disease processes, especially obstructions. In addition it can provide information regarding renal function. Difficulties associated with pyelography include worsening of ARF due to the hyperosmolarity of the contrast agent and inadequate study quality due to poor uptake of contrast in oliguric or anuric states. Antegrade pyelography may be a better choice for ureteroliths. Computed tomography or magnetic resonance imaging can add information about architecture and obstruction but requires anesthesia.

135.6.3 Other Diagnostic Modalities

Measurement of GFR (e.g., iohexol clearance, endogenous creatinine clearance, scintigraphy) can be difficult or time consuming to perform, and some techniques are subject to limited availability. Because the renal function tends to change rapidly, these studies have limited applicability in the initial treatment of ARF. Ethylene glycol intoxication is an emergency situation that requires immediate specific therapy, making accurate and timely diagnosis crucial, and a commercially available in-house test kit is available (see Chapter 78, Ethylene Glycol).

Leptospirosis titers detect an antibody reaction to the organism or vaccine. There is considerable cross-reactivity among serovars. Titers may be negative within the first 7 to 10 days; a fourfold rise after 2 to 4 weeks confirms infection. A single titer of 1:800 or greater with appropriate clinical signs in the absence of recent vaccination (or titers to nonvaccinal serovars) is also suggestive. Cats are resistant to leptospirosis. A polymerase chain reaction assay on urine has been developed for rapid early diagnosis in dogs.[4] Serologic tests for other infectious disease known to cause ARF, such as Rocky Mountain spotted fever *(Rickettsia rickettsii), Ehrlichia canis,* Lyme disease *(Borrelia burgdorferi), Babesia,* or *Leishmania,* may be useful in certain areas or when there are other consistent clinical or pathologic signs, although a positive titer does not prove causality of ARF.

A renal fine-needle aspirate can confirm the presence of lymphosarcoma but its absence cannot reliably be documented this way. The risk of bleeding is low, but possible. Renal biopsy can be obtained via percutaneous ultrasonographically guided needle biopsy, laparoscopy, or surgical wedge biopsy through a keyhole incision in the flank. A renal biopsy may confirm etiology (i.e., ethylene glycol toxicity, renal lymphosarcoma, or it may show acute tubular necrosis. The risk of bleeding when uremia is severe is high because of the thrombocytopathy.

135.7 TREATMENT

Treatment of ARF involves therapy for azotemia, therapy for extrarenal manifestations, supportive care and, in some cases, therapy specific to the underlying disease process.

135.7.1 Fluid Therapy

Dehydration deficits should be replaced with a balanced polyionic solution such as lactated Ringer's solution or Plasmalyte. Ultimately, the fluid choice must be guided by monitoring sodium concentration because the degree of free water loss relative to sodium loss varies greatly in patients with ARF. The guiding principle in treating a sodium disorder is to reverse it at the same rate at which it developed, because rapid increases or decreases in sodium concentration may cause central nervous system (CNS) dysfunction. Colloidal support (hydroxyethyl starch [hetastarch], dextran, or plasma) may also be indicated.

Determining the amount of fluid to use in ARF requires frequent reassessment of the patient's status. The calculated amount for rehydration (percentage of dehydration × body weight (kg) = fluid deficit in liters) is usually administered over 4 to 24 hours. If the patient appears hydrated, give 5% of body weight to account for undetectable dehydration. If the patient is anuric or oliguric, fluid administration should be guided by volume of urine output. Patient output includes insensible loss (respiration, stool) plus urine output plus ongoing losses (vomiting, diarrhea, nasogastric suctioning, fluid exudation into wounds). Insensible loss is 22 ml/kg q24h. To measure urine output, use a urinary catheter and record volume produced at least every 6 hours. Ongoing losses, such as vomiting, diarrhea, and yield from gastric suction, can be measured but usually are estimated (see Chapter 204, Urine Output).

To write treatment orders for intake and output using two intravenous catheters, the daily insensible loss is divided by 4 to determine the 6-hourly dose of intravenous fluid for one catheter. This fluid can be used to deliver any drugs that need to be given by constant rate infusion (CRI) (metoclopramide, lidocaine), being cognizant of drug incompatibilities. For the replacement fluid dosage, a volume based on estimate of the patient's needs is selected. The fluid rate is then recalculated every 6 hours. Use the previous 6-hour urine output volume plus an estimate of losses during that period (vomiting and diarrhea) as the volume to deliver over the next quarterly dose in the second catheter. This method avoids having to recalculate the dosage for the CRI infusion every 6 hours. If only one intravenous catheter is available, the amount of medication to be administered by CRI over 6 hours is calculated. This amount is added to the fluid volume required over the next 6 hours (6 hours of insensible losses + previous 6-hour urine output). The total volume is divided by 6 to get the hourly rate for the CRI.

An anuric patient should receive fluid administration to replace insensible loss only. If the patient is overhydrated, even that is withheld. Overhydration in an anuric patient or inability to induce diuresis in an oliguric or anuric patient is a clear indication for some form of dialysis, which is the only other effective therapeutic option.

Monitoring fluid status is an ongoing process that must be repeated throughout the day. Monitoring skin turgor takes no special equipment, but the clinician should be wary of patients with vasculitis or hypoproteinemia, who may be unable to retain fluid within the vascular compartment. Body weight should be measured at least twice daily. Following trends in packed cell volume, total solids, and blood pressure can give a relative indication of volume status. Central venous pressure measurement is useful in oliguric patients, although the correlation between central venous pressure and pulmonary vascular pressure (and development of pulmonary edema) is not perfect.

Urine volume can be determined by a variety of methods, including (1) urinary catheter and closed collection system, (2) collection of naturally voided urine, (3) metabolic cage, (4) weighing cage bedding and litter pans (1 ml of urine = 1 g), and (5) using body weight to verify accuracy. Urine volume can be categorized as anuria (none to negligible amount), oliguria (<0.5 ml/kg/hr), or polyuria (>2 ml/kg/hr).

135.7.2

Diuretics

There is no evidence that diuretics improve the outcome of ARF, and some surmise that the ability to respond to diuretics is a marker of less severe renal injury associated with a better prognosis. In humans, an increase in urine output after diuretic administration delays referral for dialysis, perhaps inappropriately.[5] However, in veterinary medicine where dialysis is not as readily available to control fluid volume, diuretic use that leads to increased urine output may enhance the ability to administer the volume of other medications or nourishment that are recommended (see Chapters 7 and 180, Oliguria and Diuretics, respectively).

135.7.3

Acid-Base and Electrolyte Balance

A variety of acid-base and electrolyte disturbances occur commonly in ARF. Hyperkalemia can be an immediately life-threatening electrolyte disorder. Renal excretion is the primary mechanism for removing potassium from the body. The increase in extracellular potassium changes the electrical potential of excitable cells. The myocardium is relatively resistant compared with the conduction cells. Typical electrocardiographic changes include bradycardia, tall spiked T waves, shortened QT interval, wide QRS complex, and a small, wide, or absent P wave. Severe hyperkalemia can lead to a sine wave, ventricular fibrillation, or standstill.

Treatment consists of insulin (0.5 U/kg regular insulin IV) to translocate potassium intracellularly. It takes up to 30 minutes to have an effect. Dextrose induces endogenous insulin release in nondiabetic patients and prevents hypoglycemia when insulin is administered. It is given at 0.5 g/kg IV or 1 to 2 g per unit of insulin given and 1 to 2 g per unit in the next dose of intravenous fluids. Metabolic acidosis causes an extracellular shift of potassium as hydrogen ions increase intracellularly. Correction of metabolic acidosis with bicarbonate allows an intracellular shift of potassium as the hydrogen ions are combined with bicarbonate and removed. The dosage of sodium bicarbonate is based on the base deficit or 2 mEq/kg IV. Calcium gluconate 10% (0.5 to 1 ml/kg IV to effect, given slowly) can be used in critical situations to restore membrane excitability without decreasing potassium concentration. It has an effect in 10 minutes, which can buy time for potassium-lowering maneuvers to work. During infusion the electrocardiogram must be monitored, and the infusion slowed or stopped if the arrhythmia worsens. Dialysis is the only method that actually removes potassium from the body.

Metabolic acidosis is a common acid-base disturbance in renal failure. Daily hydrogen ion load is excreted with NH_3 as NH_4^+. With renal failure, the kidneys are unable to excrete hydrogen ions and cannot reabsorb bicarbonate. There may be some contribution from lactic acidosis from dehydration and poor perfusion. Treatment with sodium bicarbonate is geared toward causing acid (H^+) to combine with bicarbonate HCO_3^-, which dissociates to water and carbon dioxide. If the lungs are unable to eliminate the carbon dioxide, the reaction does not proceed. Bicarbonate administration in this situation can increase the partial pressure of carbon dioxide and can lead to paradoxical CNS acidosis. This is due to the ability of carbon dioxide to diffuse into the CNS, where it can be converted back to acid.

Treatment is also contraindicated with hypernatremia. Sodium bicarbonate therapy usually is reserved for patients with a pH less than 7.2 or bicarbonate level less than 12 mEq/L. The bicarbonate dosage can be calculated from the formula:

$$0.3 \times \text{ body weight}(\text{kg}) \times \text{ base deficit } = \text{ bicarbonate}(\text{mEq} / \text{L})$$

where the base deficit = 24 – patient bicarbonate. Give one fourth to one third of the dose intravenously and an additional one fourth in the intravenous fluids over the next 4 to 6 hours. Adjust any subsequent doses based on serial blood gas determinations.

Symptomatic hypocalcemia (tetany) occurs infrequently in patients with ARF. The minimum dose of calcium gluconate that controls clinical signs should be used to prevent precipitation with phosphorus. Calcium gluconate 10% can be used at a dosage of 0.5 to 1.5 ml/kg IV over 20 to 30 minutes. As when treating hyperkalemia, monitor the electrocardiogram during infusion.

135.7.4 Extrarenal Manifestations of Uremia

Vomiting is common with ARF. Ranitidine (0.5 mg/kg IV q24h), famotidine (0.5 to 1 mg/kg IV q24h in dogs, SC in cats), and cimetidine (5 to 10 mg/kg IV slowly q8h in dogs, q12h in cats) are histamine-2 (H_2) blockers that have been used to decrease gastric acid production. Famotidine can cause hemolysis when administered intravenously to cats. The dosage for H_2 blockers in renal failure is lower because these drugs are eliminated by renal clearance.

Omeprazole is a proton pump blocker that is absorbed in the small intestine. If capsules must be split, the drug should be dissolved in sodium bicarbonate to protect it from degradation in the stomach.[6] GI protectants help heal ulcers that have already formed. Sucralfate (0.25 to 1 g PO q6h) binds to the ulcerated surface, works best in an acid environment, and should be given 2 hours before antacids.

Because uremic toxins directly affect the chemoreceptor trigger zone in the CNS, causing nausea and vomiting, centrally acting antiemetics occasionally are needed to control intractable vomiting in the patient with ARF. Metoclopramide (0.2 to 0.4 mg/kg SC q8h) is a central dopamine antagonist that is effective in decreasing vomiting in many cases. It should not be administered concurrently with dopamine. Phenothiazine derivatives such as chlorpromazine (0.2 to 0.5 mg/kg IM or SC q6-8h) and prochlorperazine (0.1 to 0.5 mg/kg IM or SC q8-12h) have hypotensive and sedative side effects. Experience with serotonin antagonists such as ondansetron (0.1 to 0.3 mg/kg IV q8-12h) and dolasetron (0.5 mg/kg PO, SC, or IV q24h) is limited, but anecdotally favorable, although these drugs are expensive. Cisapride (0.1 to 0.5 mg/kg PO q8-12h) is used as a prokinetic agent to treat delayed gastric emptying.

Bradycardia from increased vagal tone can worsen during a vomiting episode, leading to syncope or cardiac arrest. Anticholinergic medications such as glycopyrrolate (0.005 to 0.01 mg/kg IV or IM, or 0.01 to 0.02 mg/kg SC q8-12h) should be considered when this occurs.

Nutritional support in the early stages of ARF decreases morbidity in human studies. Enteral feeding is often limited by the vomiting frequently seen with renal failure. However, for those patients in which vomiting is not present or controlled pharmacologically, nasoesophageal, nasogastric, esophagostomy, or percutaneous endoscopic gastrostomy tubes can be used. If vomiting cannot be controlled, partial or total parenteral nutrition should be a consideration. In patients who are anuric or oliguric, the volume instilled, whether enterally or parenterally, must be taken into consideration and constitutes a relative contraindication unless there is a method of fluid removal (i.e., dialysis). Phosphate binders (i.e., aluminum hydroxide, aluminum carbonate, calcium acetate) administered concurrently with enteral feedings may decrease phosphate absorption.

Dialytic support may be the only effective treatment for uremia in an oliguric or anuric patient or in patients whose disease is refractory to conventional medical treatment (see Chapter 137, Hemodialysis and Peritoneal Dialysis).

Once diuresis has been established, polyuria can be quite profound. Monitoring urine production to prevent inadequate fluid administration is necessary in this situation, as well as with oliguria or anuria. Weaning these patients off of IV fluids is a crucial step. When the azotemia has been controlled and the patient seems stable, the fluid dosage can be decreased by 10% to 20% per day. If the urine output diminishes by a corresponding degree and the azotemia does not return, continue tapering slowly. If the urine output does not diminish, the kidneys are unable to regulate fluid balance, and further reduction in the fluid administered will lead to dehydration. It can take weeks for the kidneys to regain the ability to control fluid volume, but a rule of thumb is to taper fluids over the same length of time it took to diurese them. Furosemide can be tapered by 25% to 50% per day, with close monitoring to ensure continued adequate urine output.

135.7.5 Specific Treatments

In many cases of ARF, the exact etiology is not known initially, and therapy is aimed at treating the uremia and its manifestations. However, some causes of ARF have specific treatments. Penicillin G or ampicillin (22 mg/kg q6h) is the antibiotic of choice for leptospiremia, although doxycycline is also effective in the leptospiremic phase. The carrier state can be eliminated using doxycycline (5 mg/kg q12h for 2 weeks).

Antidotes for ethylene glycol (4 methylpyrazole [4-MP, Antizol-Vet] or alcohol) must be administered shortly after ingestion to be effective (see Chapter 78, Ethylene Glycol).

135.8 PROGNOSIS

Overall mortality from ARF in dogs is about 60%.[7] In the dogs that survive, approximately 60% have chronic renal failure, and only 40% recover normal renal function.[7] In cats, mortality is about 40% to 50%, with approximately 50% of survivors left with chronic renal failure.[8] Certain subsets of patients have a better prognosis. Approximately 82% to 86% of dogs with leptospirosis survived in one series.[9] Patients with polyuria have a better outcome than those with oliguria or anuria.[8,10]

135.9 SUGGESTED FURTHER READING*

CA Adin, LD Cowgill: Treatment and outcome of dogs with leptospirosis: 36 cases (1990–1998). *J Am Vet Med Assoc*. **216**, 2000, 371, *One of several articles on leptospirosis containing much clinically useful information*.

LD Cowgill, T Francey: Acute uremia. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, Philadelphia, *An excellent comprehensive review of ARF*.

S Worwag, CE Langston: Retrospective, acute renal failure in cats: 25 cases (1997–2002). *J Vet Intern Med*. **18**, 2004, 416, *An abstract presenting outcome data and some predictors of outcome in cats with ARF from a variety of causes and severity*.

* See the CD-ROM for a complete list of references.

136 Chapter 136 Chronic Renal Failure

Catherine E. Langston, DVM, DACVIM

Test	Frequency		
Physical Examination	3 to 6 Months	2 to 3 Months	Monthly
Chemistry Panel	3 to 6 Months	2 to 3 Months	Monthly
CBC	6 Months	2 to 3 Months	1 to 2 Months
Urinalysis	6 Months	6 Months	3 Months
Urine Culture	6 Months	6 Months	3 Months
Blood Pressure	3 to 6 Months	3 Months	3 Months

136.1 KEY POINTS

- Chronic renal disease or failure (CRF) is one of the most common reasons for older cats to be presented to the veterinarian, but is also commonly seen in dogs and in young animals.
- Many drugs and therapies are available for management of CRF, but there is no cure. The goal of therapy is to slow progression and to improve the pet's sense of well-being (quality of life).
- Dietary therapy decreases the number of uremic crises and decreases mortality. All pets with CRF should be encouraged to eat a renal diet if there are no contraindications (such as dietary allergies).
- As uremia progresses and the number of uremic complications increases, the number of medications to control complications increases. The nursing care involved may require a substantial time commitment from the owner.

136.2 INTRODUCTION

Chronic renal failure (CRF) is a common disease in cats and dogs. Because each nephron works as a unit, if the glomerulus is damaged irreversibly, the associated tubule will degenerate and vice versa. As nephrons are lost, the remaining nephrons hypertrophy. Although initially adaptive, glomerular hypertension damages the nephron, leading to further nephron loss. After a certain amount of damage has been sustained, renal failure may be progressive despite resolution of the initiating cause. As the renal damage progresses, azotemia develops, and eventually signs of uremia appear.

136.3 ETIOLOGY

The chronic lymphoplasmacytic interstitial nephritis that we see commonly, especially in older cats, is probably not a single entity, but the end result of any kind of renal insult. Differential diagnoses for CRF include tubulointerstitial nephritis, renal dysplasia (young animals), polycystic kidney disease (Persians, other longhair cats, less frequent in domestic shorthair cats), chronic pyelonephritis, nephrolithiasis or ureterolithiasis, infarction, lymphoma, glomerulonephritis, amyloidosis, and incomplete resolution of acute renal failure.[1]

136.4 EPIDEMIOLOGY

CRF can affect cats of any age but is more common in older cats. The incidence approaches 15% in cats over 15 years of age. Symptomatic cats tend to be older than asymptomatic cats (mean age 12.5 to 14.5 years versus 8.3 years).[2] Although CRF occurs less commonly in dogs, the incidence also increases with age.

136.5 CLINICAL PRESENTATION

136.5.1 Asymptomatic

In some patients, mild and asymptomatic azotemia is discovered incidentally, perhaps in conjunction with geriatric or dental screening. The asymptomatic pet with very mild elevations in blood urea nitrogen (BUN) or creatinine, that is maintaining body weight and appropriate hydration, may not need treatment other than diet, although routine monitoring is indicated.

136.5.2 Symptomatic

Mild clinical sings may be present for months to years (especially polyuria, polydipsia, and weight loss) before examination. In pets presented for evaluation because of early signs of renal failure, outpatient management is usually sufficient without the need for a hospital stay. A markedly dehydrated pet with severe uremic syndrome that has decompensated will likely need hospitalization for intensive therapy, including intravenous (IV) fluid administration. Once the uremic crisis is controlled, however, continued treatment at home will help delay another crisis.

Common signs include polyuria and polydipsia, weight loss, anorexia, vomiting, lethargy or depression, halitosis, dysphagia or oral discomfort, and weakness. Common physical examination findings include thin body, dehydration, abnormal kidney size or shape, heart murmur, oral ulceration, gingivitis, halitosis, hypothermia, and pale mucous membranes. Severely affected animals may suffer from altered consciousness, seizures, or bleeding problems, or be moribund.

136.6 DIAGNOSIS

The combination of historical and physical examination findings frequently leads to a clinical suspicion of CRF. Diagnostic evaluation can confirm the diagnosis, occasionally indicate the underlying cause, and detect uremic complications.

136.6.1 Laboratory Testing

Common laboratory abnormalities include azotemia, hyperphosphatemia, hypokalemia, metabolic acidosis, and hypercalcemia or hypocalcemia, although the ionized calcium level usually is normal.

Lack of erythropoietin, a hematopoietic hormone, leads to a nonregenerative anemia. Chronic inflammation or iron deficiency from chronic gastrointestinal (GI) blood loss may contribute. Some animals have an acute anemia (that may be partially regenerative) from acute blood loss from GI ulceration. The platelet count is usually normal, although platelet function may be impaired with uremia. A buccal mucosal bleeding time may be prolonged, but coagulation panel (prothrombin time and partial thromboplastin time) results are expected to be normal.

Poorly concentrated urine (urine specific gravity <1.035 in cats, <1.030 in dogs) with azotemia in the absence of urinary obstruction defines CRF. Active urine sedimentation (white blood cells, red blood cells, bacteria) may indicate urinary tract infection as a cause or consequence of CRF. A positive urine culture result may indicate pyelonephritis, although a negative urine culture result does not eliminate pyelonephritis as a cause of CRF. Routine urine culture is recommended even in the absence of lower urinary tract signs or active urine sedimentation because cats with CRF may have silent urinary tract infections. The urine protein-to-creatinine ratio is usually normal (<0.5) in cats with CRF, and varies in dogs depending on the inciting cause. Microalbuminuria indicates renal damage but is not specific for cause, whether primary or secondary. The role of microalbuminuria in monitoring or treating CRF is not yet established.

136.6.2 Imaging

Abdominal radiographs may show abnormal kidney size or shape. Approximately 33% of cats with CRF have small kidneys, 33% have normal-sized kidneys, and 33% have large kidneys.[3] Nephroliths or ureteroliths may be readily apparent, although renal function may be normal. It is also common for obstructing ureteroliths that are causing clinically significant renal damage to be smaller than the resolution limits of radiography.

Abdominal ultrasonography frequently reveals diminished renal architecture due to replacement of renal tissue with fibrosis. Other changes that may be readily identified include renal mineralization or nephroliths (although these may be missed on ultrasonography), hydronephrosis, polycystic kidney disease, and perinephric pseudocysts.

136.6.3 Other Diagnostic Modalities

Hypertension occurs in 20% to 30% of dogs and cats with CRF.[4,5] Artifactually high blood pressure (“white coat hypertension”) may be minimized by measuring blood pressure before physical examination or other procedures and selecting a calm environment, with the owner present during measurement. Renal biopsy is indicated primarily for renomegaly to evaluate for lymphoma, feline infectious peritonitis, and early glomerulonephritis. Uremia increases the risk of bleeding due to platelet dysfunction. Measurement of glomerular filtration rate rarely is used when azotemia is present, although with the advent of clinically practical methods of measuring glomerular filtration rate (i.e., plasma iohexol clearance, plasma exogenous creatinine clearance), this test is being used more commonly to diagnose early renal disease. Parathyroid hormone concentration may be elevated if renal secondary hyperparathyroidism is present.

136.7 TREATMENT

Many drugs and therapies are available for treatment of CRF. The goal of therapy is to slow progression, to minimize hospitalization time, and to improve the pet's sense of well-being (quality of life).

136.7.1 Hospitalized Patient

Decompensated cats (e.g., dehydrated, anorexic, vomiting) may benefit from hospitalization.

136.7.1.1 Fluid Therapy

Although subcutaneous fluid therapy is appropriate for outpatient treatment, the large volume of fluid required by animals in a uremic crisis mandates the intravenous route. A balanced polyionic fluid (i.e., lactated Ringer's solution, Plasmalyte) is generally appropriate. The fluid deficit is calculated (% dehydration × body weight [kg] = volume of deficit in liters) and generally is replaced over 12 to 36 hours, although some situations may necessitate more rapid replacement (i.e., hemodynamic instability or collapse, uncertain urine production capability) or slower replacement (i.e., cardiac disease). In addition to replacing the fluid deficit, a maintenance rate (66 ml/kg q24h) of fluid administration should be added. If polyuria is dramatic or if there are significant other losses (such as vomiting), the fluid rate will have to be adjusted upward accordingly. If the patient is hydrated, give maintenance fluids plus 5% body weight per 24 hours to promote diuresis.

Once the prerenal component of the azotemia has resolved, the serum creatinine concentration will usually decrease by at least 1 mg/dl per day (monitored generally q48h). When the creatinine concentration reaches a baseline value (i.e., no longer decreasing despite IV fluid therapy), fluids should be tapered in preparation for patient discharge. Aggressive diuresis should be tapered gradually over about 2 to 3 days.

136.7.1.2 Electrolytes and Acid-Base Balance

Because hypokalemia is common with CRF, most cats and many dogs benefit from potassium supplementation in the intravenous fluids. The amount of supplementation can be based on calculations of potassium deficit determined from serum potassium levels or, more simply, standard concentrations can be added to intravenous fluids based on serum potassium concentration (Table 136-1). If the amount of fluid administration is large, it is important not to exceed a rate of potassium supplementation of 0.5 mEq/kg/hr to avoid adverse cardiac effects.

If the blood pH remains below 7.2 after correcting dehydration and perfusion (and thus any lactic acidosis component), intravenous sodium bicarbonate therapy can be considered. The bicarbonate dosage can be calculated from the formula:

$$0.3 \times \text{Body weight}(\text{kg}) \times \text{Base deficit} = \text{Bicarbonate}(\text{mEq})$$

where the base deficit = 24 – patient bicarbonate level. Give one fourth to one third of the calculated dose intravenously over 30 minutes and an additional one fourth in intravenous fluids over the next 4 to 6 hours. Adjust any subsequent doses based on serial evaluation of blood gas determinations. Bicarbonate therapy is contraindicated if sodium concentration or partial pressure of carbon dioxide is elevated.

136.7.1.3 Uremic Manifestations

Therapy for uremic gastritis is indicated frequently in a uremic crisis. Treatment is similar to that used for ARF (see Chapter 135, Acute Renal Failure).

136.7.1.4 Nutrition

If anorexia persists after the patient is rehydrated or a prolonged recuperative period is anticipated, feeding tube placement is strongly recommended. Nasogastric or nasoesophageal tubes are easy to place and provide appropriate short-term support (1 to 2 weeks). Esophagostomy tubes are also relatively easy to place and may make the transition to home life smoother. Percutaneous endoscopic gastrostomy tubes can also be used similar to esophagostomy tubes. Some cats and occasional dogs will respond to appetite-stimulating drugs, including cyproheptadine (1 to 2 mg/cat, 0.3 to 1.1 mg/kg in dogs PO q12h, 30 minutes before meals) or oxazepam (2 mg/cat PO q12h).

136.7.2 Long-Term Management

Outpatient therapy is appropriate for pets that are in a compensated state. This includes animals that are eating and drinking with minimal vomiting and those who have stabilized during hospitalization for a uremic crisis. This long-term management generally is undertaken by the primary veterinarian.

Table 136-1 Potassium Supplementation Rates[16]

Serum Potassium (mEq/L)	mEq KCl per Liter of Fluids
3.5 to 4.5	20
3 to 3.5	30
2.5 to 3	40
2 to 2.5	60
<2	80

KCl, Potassium chloride.

136.7.2.1 Dietary Therapy

Restricted quantity (but high-quality) protein and restricted phosphorus diet ("renal diet") slows progression, prolongs survival, and decreases signs of uremia.[6,7] There are many different brands of renal diet, and palatability varies with the patient. Homemade diets may also be used. Dietary therapy should be recommended for all dogs and cats with CRF (symptomatic and asymptomatic). Commercial diets include Hill's K/D, Eukanuba Multi-Stage Renal Diet for cats and Early Stage or Late Stage for Dogs, Royal Canin Renal LP or MP Diet, Royal Canin Modified Formula, and Purina Veterinary Diets CNM NF. Avoid acidifying diets in cats. Acceptance of diet changes can be problematic, particularly in severely affected patients. Renal diets should be introduced when uremia has been minimized. Maintaining adequate caloric intake to avoid weight loss takes precedence over nutrient composition of the diet, and a feeding tube allows administration of adequate amounts of the best diets, independent of the pet's appetite, and is strongly encouraged for pets with anorexia and weight loss.

136.7.2.2 Fluid Therapy

Pets with chronic dehydration or persistent signs of uremia may benefit from SC fluid therapy. Owners can be taught to administer fluids at home. Dosage is empiric, based on subjective assessment of patient's well-being and hydration status. Lactated Ringer's solution and 0.9% saline are the best choices; solutions that contain dextrose should be avoided. A typical starting dosage for a cat is 100 to 125 ml q24-72h. Pleural effusion may develop in cats receiving large dosages (200 to 400 ml q24h). Animals that do not require ongoing SC fluid therapy may benefit from intermittent treatment during times of stress (exacerbation of uremia, other illness, boarding, traveling).

136.7.2.3 Uremia Management

A restricted phosphate diet may be sufficient to control hyperphosphatemia during early stages. If not, a phosphate binder should be used to bind phosphorus in ingested food and prevent absorption. The dosage of aluminum hydroxide or aluminum carbonate (30 to 90 mg/kg q24h divided and administered with meals) is titrated based on serum phosphorus concentration. Liquid forms are more effective than tablets, but aluminum carbonate capsules (opened and mixed with food) may be more palatable. Aluminum-containing phosphate binders may interfere with absorption of other medications such as antibiotics. Calcium acetate (60 to 90 mg/kg q24h) is an alternative that does not contain aluminum, but hypercalcemia is a possible side effect. New phosphate binders (sevelamer hydrochloride, lanthanum carbonate) are available for humans, but veterinary experience with them is limited.

Animals with CRF have elevated gastrin levels, and histamine blockers commonly are used to decrease gastric acidity, which may be associated with anorexia, nausea, or vomiting.[8] Commonly used drugs include famotidine (0.5 to 1 mg/kg PO q24h) and ranitidine (0.5 to 2 mg/kg PO q24h). Omeprazole is a proton pump blocker (0.5 to 1 mg/kg PO q24h). It is supplied as capsules that prevent degradation in the stomach before absorption in the small intestine. If the capsules must be reformulated, the pharmacist should suspend the drug in sodium bicarbonate to protect it. Antiemetics may be useful in persistently vomiting animals. Metoclopramide (0.2 to 0.4 mg/kg PO q6-8h) acts as motility modifier and central antiemetic. There is limited 596 experience with 5-HT (serotonin) 597 antagonists (ondansetron 0.1 mg/kg PO q12-24h, dolasetron 0.5 mg/kg PO q24h), although anecdotally they seem to help in animals with intractable vomiting. GI ulceration may be suspected if hematemesis, melena, anemia, or an elevated BUN-to-creatinine ratio are present. Sucralfate (0.25 to 1 g PO q8-12h) can be used for 1 to 2 weeks or until clinical signs resolve.

Animals with low serum potassium concentrations should receive supplementation. Oral supplements include potassium gluconate (2 to 6 mEq per 4.5 kg q24h) and potassium citrate (50 to 75 mg/kg PO q12h). Potassium citrate also contributes to acidosis treatment.

Consider treatment of metabolic acidosis if total carbon dioxide is less than 15 to 16 mEq/L or blood pH is lower than 7.2. Choices include potassium citrate (50 to 75 mg/kg PO q12h) or sodium bicarbonate (8 to 12 mg/kg PO q8-12h). Many cats do not tolerate sodium bicarbonate therapy well.

The goal of long-term management of hypertension is to maintain the systolic blood pressure below 140 to 160 mm Hg. Amlodipine (0.625 to 1.25 mg/cat, 0.2 to 0.4 mg/kg in dogs, q12-24h) is an effective first-choice drug in about 60% of cats, and is a logical first choice in dogs if there is no proteinuria.[9] Start at the low end of the dosage range and titrate upward as needed. If amlodipine is ineffective as a single agent or if proteinuria is present, an angiotensin-converting enzyme (ACE) inhibitor such as benazepril (0.25 to 0.5 mg/kg PO q12-24h) or enalapril (0.25 to 0.5 mg/kg PO q12-24h) is indicated. Monitor BUN, creatinine, and electrolytes 1 week after starting therapy with an ACE inhibitor or when increasing the dose. β-Blockers (e.g., atenolol PO 6.25 to 12.5 mg/cat q24h, 0.25 to 1 mg/kg q12-24h in dogs) may be used if tachycardia is present.

Higher levels of proteinuria predict a worse outcome in dogs with CRF.[10] Treatment with an ACE inhibitor decreases proteinuria in dogs with glomerulonephritis and mild CRF.[11] Significant proteinuria is uncommon in cats with CRF. A urine protein-to-creatinine ratio greater than 1 is considered abnormal, but some suggest that a level greater than 0.4 in cats should prompt intervention.[12] The small percentage of cats with significant proteinuria do seem to benefit from ACE inhibition, whereas ACE inhibition has no statistical effect on survival times in cats without proteinuria.[13]

A low dosage of calcitriol (0.75 to 5 ng/kg q24h) decreases mortality in dogs with CRD and is postulated to help by decreasing parathyroid hormone production.[14] Studies evaluating low-dosage calcitriol in cats are underway. Administration to a patient with hyperphosphatemia is contraindicated because of the risk of soft-tissue mineralization. Serum calcium levels should be monitored carefully because calcitriol may cause hypercalcemia. Careful attention to dosage is necessary because it is measured in nanograms per kilogram, whereas calcitriol is supplied in micrograms and must be reformulated accurately to avoid overdosing.

136.7.2.4

Anemia Management

If the patient has severe clinical signs of anemia, a transfusion (whole blood or packed red blood cells) may be necessary for immediate control of signs. Transfused cells usually are destroyed within 2 to 3 weeks, and a longer term solution is then needed. Human recombinant erythropoietin (Epogen, Procrit) is effective in stimulating erythropoiesis in dogs and cats. Its use should be restricted to patients symptomatic for anemia (weakness, anorexia, exercise intolerance, tachycardia, heart murmur) because of the risk of antibody formation. Up to 25% of dogs and cats thus treated will develop antibodies, which may result in euthanasia because of transfusion dependence or transfusion reactions.

The starting dosage of 100 U/kg SC is administered initially 3 times a week, then decreased to twice a week when patient reaches the bottom of the target range (packed cell volume [PCV] 25% to 30% for cats, 30% to 35% for dogs). The maintenance dosage is 50 to 100 U/kg SC 1 to 2 times per week. A newer modified erythropoietin product, darbepoeitin, will also stimulate erythropoiesis in dogs and cats (0.45 μg/kg SC once weekly, decreasing to once every 2 to 3 weeks). The risk of antibody formation is not known, but appears to be lower than the risk with Epogen or Procrit. The PCV should be monitored each week initially and the dosage adjusted as needed. Adequate iron stores are necessary for an optimal response, and iron administration usually is required during the initial treatment period. Iron sources include iron dextran (50 mg/cat, 10 to 20 mg/kg in dogs, deep IM injection monthly), ferrous sulfate (50 to 100 mg/cat, 100 to 300 mg/dog PO q24h). Iron proteinate (Pet-Tinic, 10 to 20 ml/dog, 3.5 to 7 ml/cat PO q24h) requires an exceedingly large volume to provide sufficient iron. Animals receiving erythropoietin therapy will generally show a response (increased hematocrit, reticulocytosis) after 2 weeks of treatment, unless extraneous factors causing resistance are present (i.e., GI hemorrhage, infection, or chronic inflammation).

136.7.2.5

Other Therapies

Renal transplantation may be appropriate for some cats and some owners. The greatest chance of success is in mildly to moderately azotemic cats without concurrent illness or infection. Transplantation should be considered at the point of early decompensation (when the cat can no longer maintain weight, signs of uremia are not controlled by interventions) and is not an emergency or salvage procedure. Hemodialysis is available in a limited number of places. Because of ongoing need (2 to 3 times a week throughout life) and cost, long-term hemodialysis is not commonly used, but excellent results may be obtained in certain cases. Complications associated with peritoneal dialysis (especially catheter occlusion and peritonitis) have limited its use to acute settings.

136.8 MONITORING

The frequency of monitoring depends on the patient's condition and location. Any change in the clinical condition should prompt a reevaluation.[15] General guidelines are listed in Table 136-2. Clinical signs of hypokalemia, hyperphosphatemia, anemia, and hypertension may not occur until they are severe and devastating; early interventions can be based on detection by routine screening. PCV and blood pressure should be measured weekly in pets during the initial phase of erythropoietin therapy (while receiving the drug 3 times a week). As the PCV stabilizes and the dosage is decreased, the frequency of monitoring can be decreased to monthly. Animals with CRF are predisposed to urinary tract infection, which may be asymptomatic. Routine urine culture is recommended even in the absence of clinical signs. The effect of most antihypertensive medications can be assessed about 1 week after dosage adjustments.

Table 136-2 Monitoring Guidelines for Chronic Kidney Disease

	Mild CKD	**Moderate CKD**	**Severe CKD**
Cats	Creatinine <2.8 mg/dl	Creatinine 2.8 to 5 mg/dl	Creatinine >5 mg/dl
Dogs	Creatinine <2.1 mg/dl	Creatinine 2.1 to 5 mg/dl	Creatinine >5 mg/dl
	Not on SC fluids	SC fluids <4 × per wk	Daily SC fluids

CBC, Complete blood count; *CKD,* chronic kidney disease;*SC,*subcutaneous.

136.9 Prognosis

CRF is a progressive disease, but the rate of progression is highly variable. There are no known predictors of impending decompensation. Most animals will die of CRF or related complications, although some maintain stable renal function and die of unrelated causes (such as neoplasia). Cats with mild to moderate renal disease commonly survive 1 to 3 years. Survival in dogs with mild to moderate disease is approximately 1 to 2 years.[4,6] An elevated urine protein-to-creatinine ratio (>0.4 in cats, >1 in dogs) predicts shorter survival.[10,12] ACE inhibitor treatment (i.e., benazepril) prolongs survival in cats with a urinary protein-to-creatinine ratio grater than 1. Hypertension at diagnosis is prognostic of shorter survival times in dogs.[4]

136.10 SUGGESTED FURTHER READING*

FW Bell, CA Osborne: Treatment of hypokalemia. In JD Bonagura (Ed.): *Kirk's current veterinary therapy XIII: small animal practice*. ed 13, 2000, Saunders, Philadelphia, *A chapter presenting the Scott sliding scale of potassium supplementation*.

F Jacob, DJ Polzin, CA Osborne, et al.: Clinical evaluation of dietary modification for treatment of spontaneous chronic renal failure in dogs. *J Am Vet Med Assoc*. **220**, 2002, 1163, *A sentinel paper describing a definite positive clinical effect of diet on survival and uremic morbidity in naturally occurring renal failure in dogs*.

F Jacob, DJ Polzin, CA Osborne, et al.: Evaluation of the association between initial proteinuria and morbidity rate or death in dogs with naturally occurring chronic renal failure. *J Am Vet Med Assoc*. **226**, 2005, 393, *A well-designed study that showed that a urinary protein-to-creatinine ratio greater than 3 at* *diagnosis of CRF was associated with a higher risk of uremic morbidity, death from renal failure, and death from all causes*.

DJ Polzin, CA Osborne, S Ross, et al.: Chronic kidney disease. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, St Louis, *An excellent comprehensive review of all aspects of CRF*.

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* See the CD-ROM for a complete list of references

137 Chapter 137 Hemodialysis and Peritoneal Dialysis

Julie R. Fischer, DVM, DACVIM

137.1 KEY POINTS

- Hemodialysis (HD) and peritoneal dialysis (PD) are chiefly indicated to perform the excretory functions of the kidneys in patients with acute or chronic kidney failure.
- HD and PD can also be used to augment removal of certain toxins or toxicants and to remove excess water from the body in severe fluid overload.
- In HD the patient's blood is pumped through an extracorporeal circuit. Interface between blood and dialysate (and resulting solute and fluid exchange) occurs outside the body across the many dialyzer membranes.
- PD uses the peritoneal membrane as an interface between the blood and dialysate; dialysate is instilled and removed through a catheter in the peritoneal cavity.
- Indications for dialysis include severe, intractable uremia (acute or chronic), severe hyperkalemia, intractable volume overload, and some acute toxicoses.
- Both HD and PD carry morbidity and mortality risks but, when indicated, potential benefit to the patient usually outweighs the risk of therapy.

137.2 GENERAL PHYSICAL PRINCIPLES

Dialysis entails movement of solutes and water across a semi-permeable membrane according to concentration gradients. In clinical medicine, the blood interfaces indirectly with a contrived solution, termed *dialysate*. The dialysate is formulated to favor movement of waste solutes (e.g., urea, creatinine, phosphorus) out of plasma, to maintain physiologic plasma concentrations of other substances (e.g., sodium, glucose, calcium), and to replenish or load depleted solutes (e.g., bicarbonate). In hemodialysis (HD) the blood-dialysate interface is extracorporeal, across the membranes of a hollow-fiber dialyzer through which the patient's blood is pumped. In peritoneal dialysis (PD) the vessel-rich peritoneum serves as the dialysis membrane. In both, removal of solutes and excess plasma water occurs across the dialysis membranes by the processes of diffusion, ultrafiltration, and convection.[1-3]

Most solute removal during a standard HD or PD session occurs by diffusion, relying on random particular motion. Particles arbitrarily encounter dialyzer membranes and may pass through via channels. Odds of channel contact are directly proportional to a given particle type's concentration and thermodynamic energy. At equal concentrations, smaller molecules diffuse more readily than larger ones because of their higher thermodynamic energy. If concentrations of a solute equalize on both sides of the membrane (filtration equilibrium), diffusion still occurs but net transfer of that solute is zero. Maintenance of the concentration gradient, and therefore diffusion, requires continuous (HD) or periodic (PD) dialysate replacement.[1-4]

Ultrafiltration can remove excess plasma water. In HD, the outward transmembrane hydraulic pressure generated by the blood pump, plus a vacuum applied to the dialysate side, moves water from the blood across the membrane and into the dialysate.[1,2] The amount of fluid to be removed is programmed into the delivery system and is modified as needed. Hyperosmolar dialysate draws fluid into the peritoneal cavity in PD. Dialysate osmolality usually is adjusted by varying dextrose concentration; higher dextrose concentrations effect faster fluid removal.[3]

Convection, also termed *solvent drag,* refers to movement of dissolved solutes in conjunction with movement of fluid across the dialysis membrane during ultrafiltration in both HD and PD.[1-3] Convection plays a minor role in solute removal during standard dialysis and occurs only with ultrafiltration. Some HD techniques maximize convection by performing simultaneous high-rate ultrafiltration and intravenous fluid replacement. Combined with HD, this is called *hemodiafiltration* and maximizes removal of middle-molecular-weight solutes (≈12,000 kD).[1,2]

137.3 HEMODIALYSIS

HD requires repeated large-gauge vascular access, usually achieved in animals with jugular catheters. Ideally, a dual-lumen jugular catheter is placed with the catheter tip in the right atrium. For acute dialysis, a temporary catheter is placed percutaneously and usually gives 2 to 3 weeks of access. If the need for HD exceeds the functional life span of this catheter, a permanent HD catheter is placed. Permanent catheters have a Dacron cuff, placed subcutaneously between the venotomy and skin exit site. Fibroblasts migrate into the cuff, stabilizing the catheter and creating a physical barrier to bacteremia.[1,2]

Before treatment, the patient is assessed and the catheter exit site and ports cleaned meticulously. The HD prescription (dialysate formula, dialyzer and circuit, treatment time, ultrafiltration volume, target blood volume, heparinization) is designed at each treatment, based on physical and biochemical status, as well as prior treatment response. Severely azotemic patients (blood urea nitrogen [BUN] >150 mg/dl) require staged initial azotemia reduction. The urea reduction ratio (URR) is calculated as 1 − (posttreatment BUN ÷ pretreatment BUN). Typically, the first HD treatment targets a 0.3 to 0.6 URR (usually not to exceed a URR of >0.1/hr), the second treatment a 0.5 to 0.8 URR, and the third treatment a 0.9 to 0.95 URR, with treatments usually performed on consecutive days.[1,2]

Staged azotemia reduction permits cerebral acclimation to the osmolality change accompanying resolution of azotemia. 599 600 This lessens the risk of dialysis disequilibrium syndrome, a clinical manifestation of cerebral edema that varies from ataxia, altered mentation, and pupillary abnormalities, to seizure, coma, and death from brain stem herniation. Mannitol, given during initial treatments (particularly in cats), acts as prophylaxis against dialysis disequilibrium syndrome. Once renal values are lowered into the normal range, thrice-weekly HD can maintain a nonuremic state and good quality of life until renal function improves.[1,2]

Highly and specifically trained personnel are critical to safe and effective HD. Filtering and reverse osmosis provide purified water for the dialysate to minimize patient exposure to harmful agents. The dialysis delivery system monitors and regulates dialysate composition and temperature, rate of blood flow, anticoagulant delivery, blood circuit pressures, and ultrafiltration. Before treatment, dialysate and bicarbonate concentrates are connected to intake hoses, and the extracorporeal circuit and dialyzer are primed with saline or dextrans. Following systemic heparinization, the patient's catheter ports are connected to extracorporeal blood lines, and a pump draws blood into the circuit, through the dialyzer, and back to the patient. If a treatment parameter is breached, the system alarms and suspends dialysis pending correction.

During treatment, physical status and treatment parameters (e.g., flow rate, chamber pressures, ultrafiltration response) are monitored closely. Blood pressure, heart rate, and clotting times are measured every 15 to 30 minutes or as needed, and ideally venous oxygen saturation and hematocrit are monitored continuously with an in-line probe. General appearance and mentation are monitored continuously.

At the end of treatment, a rinse-back procedure returns the circuit blood to the patient. The catheter is capped in a sterile manner and the catheter lumens filled with a lock solution (usually 100 to 5000 U/ml heparin). A neck wrap protects the catheter until the next treatment. Dialysis catheters are guarded jealously and handled only by dialysis personnel. With stringent care, some dialysis catheters have been maintained in dogs for a year or longer.[1,2]

137.4 PERITONEAL DIALYSIS

PD involves little specialized equipment and is not technically difficult, but it is extremely labor intensive and demands meticulous sterile technique. PD requires insertion of an indwelling catheter into the abdominal cavity, and the degree and durability of catheter function chiefly determine success or failure of treatments. Most catheters are Silastic tubing with multiple fenestrations and one or two Dacron cuffs. The fenestrations are positioned in the peritoneal cavity; the cuffs are placed in the rectus sheath or the subcutaneous tunnel created between the point of rectus penetration and skin exit. Tissue growth into the cuffs anchors the catheter and provides a physical barrier to dialysate leakage and ascending infection. Catheter placement is performed percutaneously, laparoscopically, or via laparotomy; laparotomy gives the option of simultaneous partial or complete omentectomy, which may substantially increase and prolong catheter function. If the need for PD may exceed 24 hours, omentectomy is recommended.[3,4]

PD is accomplished by infusion of dialysate into the abdomen through the catheter, allowing the dialysate to remain for a prescribed dwell time, draining the fluid into a waste bag, and repeating the process. Each drain-infuse-dwell series is called a cycle or exchange. Exchanges can be performed with a straight transfer set, but ideally the dialysate bag, catheter, and drainage bag are connected by a closed Y system that permits drainage followed by dialysate infusion without catheter disconnection. Before drainage, a small amount of clean dialysate should be flushed through the line into the drainage bag. The abdomen is then drained and subsequently filled with fresh dialysate for the next dwell. This drain-then-infuse sequence flushes any contaminants in the system into the drainage bag instead of into the abdomen, and in humans markedly reduces occurrence of secondary septic peritonitis.[3,4]

PD solutions contain sodium, chloride, a buffer (usually lactate), varying concentrations of calcium and glucose or dextrose, and varying other additives (amino acids in some newer solutions). A simple PD solution may be made by adding dextrose (30 ml of 50% dextrose in 1 L = 1.5% dextrose solution) and heparin (250 to 2000 u/L) to lactated Ringer's solution. Adding heparin for the first days after catheter placement decreases the risk of catheter occlusion from fibrin deposition. Initial exchanges for marked azotemia or overhydration are performed every 1 to 2 hours with 30-minute to 40-minute dwell times. This high exchange frequency continues for 24 to 48 hours, or until clinical stabilization with BUN of 70 to 90 mg/dl and creatinine of 4 to 6 mg/dl. Then a less intensive schedule (e.g., exchanges 3 to 4 times per day with 4 to 6 hour dwells) is adopted.[3]

Maintenance of sterility is critically important because septic peritonitis is a common, often terminal, complication of veterinary PD. Sterile gloves should be worn during connection, disconnection, and bag changes (bag spike contamination is the most common source of peritonitis in human PD) and hands washed frequently. Cover line connections with chlorhexidine-soaked dressings during infusions and drains. Clean injection ports with chlorhexidine or alcohol before use, and use new, single-dose vials for dialysate additives.[3]

Careful monitoring of the patient and PD procedures is critical to effective and safe treatments and allows complications to be addressed at the earliest point. Critical monitoring data for PD patients should be collected and maintained in an organized fashion for analysis and future treatment planning.

137.5 DISCONTINUATION OF DIALYSIS

Dialysis, whether PD or HD, is discontinued when the patient maintains normal fluid balance and shows excretory function compatible with clinical well-being, or a targeted toxin or toxicant has been removed. Mild to moderate azotemia may persist, but the patient must be nonuremic. Many patients continue renal recovery for weeks to months after dialysis is discontinued. Nutritional support via a feeding tube may be required during that period.

137.6 VETERINARY APPLICATIONS

Dialysis may benefit companion animals in three broad circumstances: (1) when a patient cannot eliminate waste 600 solutes and fluids because of renal excretory failure, (2) in intractable fluid overload (often due to kidney or heart 601 failure), and (3) for treatment of intoxications (Box 137-1).[1-9]

137.6.1 Box 137-1 Common Clinical Indications for Hemodialysis and Peritoneal Dialysis

- Severe uremia*
- Acute uremia*
- Marked azotemia (usually BUN ≥150 mg/dl and/or creatinine ≥10 mg/dl)*
- Severe electrolyte derangement (hyperkalemia, hyponatremia or hypernatremia)*
- Severe metabolic acidosis*
- Delayed graft function following transplantation*
- Chronic (end-stage) kidney disease*
- Refractory uremia (usually BUN ≥100 mg/dl or creatinine ≥10 mg/dl)†
- Preoperative conditioning for renal transplantation†
- Finite extension of improved quality of life to allow client adjustment to diagnosis and prognosis*
- Volume overload*
- Unresponsive oligoanuria*
- Fulminant congestive heart failure*
- Pulmonary edema*
- Circulatory overload*
- Lack of response to diuretics*
- Iatrogenic fluid overload*

- Parenteral nutrition for oligoanuric animals*
- Acute toxicosis or drug overdose*
- Ethylene glycol toxicosis (both acute toxin removal and long-term management of resultant ARF)*
- Environmental or agricultural toxins†
- Accidental ingestion or overdose of many chemicals and medications†
- Miscellaneous*
- Pancreatitis‡
- Severe hyperthermia‡
- Severe hypothermia‡
- Hypercalcemia*

ARF, Acute renal failure; *BUN,* blood urea nitrogen; *HD,* hemodialysis; *PD,* peritoneal dialysis.

* HD and PD.

† HD chiefly.

‡ PD chiefly.

Most animals considered for dialysis have acute uremia, unresponsive to intravenous fluid diuresis and pharmacologic manipulation.[1-7] Uremia may be due to acute renal injury, postrenal causes, or acute exacerbation of underlying chronic renal disease, and may include life-threatening hyperkalemia or acidosis in addition to azotemia. Animals may be polyuric, oligoanuric, or have normal urine output. In dogs, common causes of acute uremia include nephrotoxic agents, infectious agents, severe systemic illness, decompensation of chronic interstitial nephritis or glomerulonephritis, and renal ischemia.[5,7,8] In cats, common causes of acute uremia include acute ureteral obstruction, nephrotoxic agents, pyelonephritis, acute exacerbation of chronic interstitial nephritis, and lymphoma.[6,7] Dialysis provides a bridge of metabolic stability for these patients, sustaining life while the kidneys undergo cellular repair or the cause of uremia is corrected (e.g., acute ureteral obstruction). Dialysis can also mitigate the signs of chronic, end-stage renal disease when conventional treatment fails, but few owners are financially able to continue such therapy indefinitely. For long-term dialysis in companion animals, HD rather than PD is the therapy of choice, if geographically available.

Ultrafiltration can manage life-threatening volume overload (e.g., due to oliguria or anuria, congestive heart failure, excessive fluid administration) in a patient unresponsive to diuretics.[1-4] Excess fluid removal can resolve pulmonary and peripheral edema and help prevent reaccumulation of body cavity effusions by reducing capillary hydrostatic pressure. Resolution of volume overload also enhances blood pressure control in these often hypertensive patients.

Dialysis is uniquely suited to the removal of toxins and toxicants. Drugs and chemicals with physical characteristics that permit passage through dialyzer membrane pores or across the peritoneal membrane can be removed from the bloodstream with HD or PD (Box 137-2).[1-4,7-10] Of particular note, ethylene glycol and its nephrotoxic metabolites are removed easily by dialysis, and if such removal is accomplished promptly and thoroughly (within 8 to 12 hours of ingestion in dogs) renal damage may be lessened or prevented entirely.[10]

137.7 RISKS AND COMPLICATIONS

Although both HD and PD carry significant risk of morbidity and mortality, patients presented for these therapies usually have a guarded to grave prognosis if not dialyzed. Both HD and PD can mitigate the metabolic crises accompanying acute renal failure and can help remove dialyzable toxins and toxicants. Part of determining a given patient's suitability for dialysis involves weighing potential risk versus potential benefit. HD risks and complications include hemorrhage, catheter-related infection or sepsis, dialysis disequilibrium syndrome, and hypotension, among others.[1,2,9] PD risks and complications include septic peritonitis, catheter occlusion and dysfunction, and dialysate leakage, among others.[3,4,7] Whether to use HD or PD in a given patient often depends on availability, because few veterinary HD centers exist. Generally veterinary PD patients remain hospitalized during therapy. HD often can be performed on an outpatient basis after initial treatments.

137.8 OUTCOMES

Overall survival for patients undergoing HD has been reported at approximately 40% to 60%; prognosis for most of these patients without dialysis is poor.[5,6,9] A review of 119 cats requiring HD reported that 62 (52%) survived, 31 (26%) were euthanized, and 26 (22%) died.[6] A similar review of 138 dogs requiring HD revealed a survival rate of nearly 40%.[5] No recent analysis of PD survival in dogs and cats is available, but an older retrospective showed survival of 6 of 25 dogs and 0 of 2 cats receiving PD for acute uremia.[7] Dialytic therapy is intensive and costly, but for patients requiring its unique capacities, it can be lifesaving.

137.8.1 Box 137-2 Compounds That Are Readily Removed From the Body by Hemodialysis, Peritoneal Dialysis, or Both

137.8.1.1 Alcohols

Ethanol*

Ethylene glycol†

Methanol*

137.8.1.2 Analgesics and Antiinflammatory Agents

Acetaminophen*

Aspirin[†]

Mesalamine (5-ASA)[*]

Morphine[‡]

Pentazocine[*]

137.8.1.3 Antibacterial Agents

Amikacin[†]

Amoxicillin (most penicillins)[*]

Cephalexin (most first generation)[*]

Cephalosporins[*] (some[†])

Cefotetan (many second-generation cephalosporins[*]; some[†])

Cefoxitin[*]

Ceftriaxone (many third-generation cephalosporins[*]; some[†])

Chloramphenicol[*]

Clavulanic acid[†]

Gentamicin[†]

Imipenem[†] and cilastatin[*]

Kanamycin[†]

Linezolid[*]

Metronidazole[*]

Neomycin[†]

Nitrofurantoin[*]

Ofloxacin[*]

Sulbactam[*]

Sulfamethoxazole[*]

Sulfisoxazole[†]

Trimethoprim[*]

Tobramycin[†]

Vancomycin[‡]

137.8.1.4 Anticonvulsants

Gabapentin[*]

Phenobarbital[†]

Phenytoin[‡]

Primidone[*]

137.8.1.5 Antifungal Agents

Dapsone[*]

Fluconazole[†]

Flucytosine[†]

137.8.1.6 Antineoplastic Agents

Busulfan[*]

Carboplatin[*]

Cisplatin[‡]

Cytarabine[‡]

Cyclophosphamide[*]

Fluorouracil (5-FU)[*]

Ifosfamide[*]

Methotrexate[*]

Mercaptopurine[*]

137.8.1.7 Antiviral Agents

Acyclovir[*]

Famciclovir[*]

Valacyclovir[*]

Zidovudine[†]

137.8.1.8 Cardiac and Vasoactive Medications

Atenolol[*]

Bretylium[*]

Captopril*

Enalapril†

Esmolol†

Lisinopril*

Metoprolol*

Mexiletine*

Nitroprusside†

Procainamide*

Sotalol*

Tocainide*

137.8.1.9 Chelating Agents

Deferoxamine*

Ethylenediamine tetraacetic acid (EDTA)†

Penicillamine*

137.8.1.10 Immunosuppressive Agents

Azathioprine*

Methylprednisone*

137.8.1.11 Miscellaneous Medications

Allopurinol*

Aminocaproic acid[†]

Ascorbic acid[†]

Carisoprodol[†]

Chloral hydrate[*]

Chlorpheniramine[*]

Diazoxide[†]

Foscarnet[*]

Iohexol[*]

Iopamidol[†]

Lithium[†]

Mannitol[†]

Meprobamate[†]

Metformin[*]

Methyldopa[†]

Minoxidil[†]

Octreotide[*]

Ranitidine[†]

Theophylline*

* Dialyzable by HD only.

† Dialyzable by PD as well as HD.

‡ Dialyzable by high-flux HD only.

137.9 SUGGESTED FURTHER READING*

LD Cowgill, T Francey: Hemodialysis. In SP DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 3, 2006, Saunders, St Louis, *The most comprehensive reference on veterinary hemodialysis, with some very technical information, but very complete source reading.*

LA Dzyban, MA Labato, LA Ross: Peritoneal dialysis. In JD Bonagura (Ed.): *Kirk's current veterinary therapy XIII: small animal practice*. ed 13, 2000, Saunders, Philadelphia, *A concise update on PD; good catheter information but few "how to" details*.

JR Fischer, V Pantaleo, T Francey, et al.: Veterinary hemodialysis: advances in management and technology. *Vet Clin North Am Small Anim Pract*. **34**, 2004, 935, *Fairly complete information on indications for and performance of HD in small animals, including materials and methodology. List of veterinary hemodialysis centers in the United States in the appendix.*

MA Labato, LA Ross: Peritoneal dialysis. In SP DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 3, 2006, Saunders, St Louis, *A clear, straightforward reference for PD with technical as well as theoretic information*.

* See the CD-ROM for a complete list of references

138 Chapter 138 Urinary Catheterization

Sean Smarick, VMD, DACVECC

138.1 KEY POINTS

- Urinary catheterization is indicated often in the critically ill patient to accurately monitor urine output. Other indications include obtaining a urine sample for analysis, performing radiographic contrast procedures, relieving an anatomic or functional obstruction, and supporting the lower urinary tract after surgery.
- Catheter-associated urinary tract infection is a potential complication of the procedure but may be limited by using placement and maintenance protocols and restricting the use of indwelling catheters to appropriate patients.
- Species, sex, and purpose of catheterization are considerations for choosing a catheter type.
- A urinary catheter usually can be inserted with topical anesthetic and, if needed, light sedation.
- Female dogs can be catheterized easily by using digital palpation of the urethral opening or direct visualization with the aid of a light source and speculum. A blind technique is often successful in small female dogs and cats.
- Indwelling urinary catheters require ongoing care, and their need in individual patients should be reevaluated daily.

138.2 INTRODUCTION

Urinary catheterization is performed for diagnostic, treatment, or monitoring purposes and often is indicated in critically ill patients. Sex and species differences may offer anatomic challenges that can be overcome with proper technique and practice. Each patient should be evaluated individually for a clear indication for the procedure, type of urinary catheter to be used, and the duration of which the catheter is to remain in place. Indications for urinary catheter placement can be grouped into those warranting a one-time or intermittent placement and those in which the catheter should be left in place.

138.3 INDICATIONS

138.3.1 Intermittent Catheterization

One-time or intermittent urethral catheterization can be used to obtain urine samples, perform radiographic contrast procedures, or relieve an anatomic or functional obstruction leading to urine retention. Samples for urinalysis may be obtained via catheterization, although bacterial and red blood cell contamination may occur.[1,2] Additionally, retrieval of small stones from the bladder has been described using urinary catheters. Urinary contrast imaging procedures, such as a contrast urethrocystogram, assess the integrity of the lower urinary tract and can help characterize bladder masses, calculi, and urethral obstructions due to neoplasia, a calculus, or a foreign body. Lastly, urethral obstructions may be relieved or bypassed with a urinary catheter. Retrohydropulsion can be used to help dislodge calculi.

138.3.2 Indwelling Catheterization

Indwelling urinary catheters allow for continuous urine collection and, based on human guidelines by the Centers for Disease Control and Prevention, are indicated for urinary obstruction, urine retention due to neurogenic bladder dysfunction, surgery of the lower urinary tract, or in critically ill patients for accurate urine output determination.[3] Simple recumbency or wishing to prevent the patient from soiling itself is not a justifiable indication.

These recommendations are made to prevent complications, namely catheter-associated urinary tract infections (UTIs).

138.4 COMPLICATIONS

138.4.1 Infectious

Catheter-associated UTIs have been reported in the veterinary literature and the incidence may exceed 50%. These infections have played a role in nosocomial outbreaks in veterinary intensive care units (ICUs) and have the potential to cause serious morbidity and mortality. Resistant bacteria such as *Klebsiella, Acinetobacter, Enterobacter, Citrobacter, Serratia, Pseudomonas* spp, and *Escherichia coli* may cause catheter-associated UTIs in veterinary ICUs and may serve as a source within the ICU for other nosocomial infections.[4-9]

Catheter-associated UTIs are thought to occur as a result of introducing bacteria into the bladder during catheter insertion. In one study, there was a 20% incidence of UTIs following a one-time catheterization in female dogs.[10] Once indwelling, the catheter provides a surface on which bacteria may migrate. This often involves a biofilm, a matrix of microorganisms and their produced glycocalyces, host salts, and proteins. Biofilms allow for the adherence of bacteria to catheter surfaces and provide protection from the host's defenses. Not surprisingly, duration of catheterization and absence of a closed collection system has been positively correlated with catheter-associated UTIs.[6]

Prophylactic or concurrent administration of antibiotics may offer short-term protection against a UTI, but organisms that are resistant to the antibiotics often emerge. Therefore routine prophylactic antibiotics are not recommended; however, they could be considered in compromised patients with anticipated short-term urinary catheter use.[4] Despite the morbidity and even mortality associated with urinary catheters, appropriate patient selection coupled with placement and maintenance protocols as described below resulted in a 10% incidence of nonresistant catheter-associated UTIs in a veterinary ICU. Most of these patients had urinary catheters placed for monitoring urine output and left in place for less than 4 days.[4]

138.4.2 Mechanical

During placement, stiff catheters or catheter stylets may cause physical trauma to the urethra or bladder. Appropriate lubrication, judicious use of force, and properly seated stylets (i.e., contained within the catheter) are indicated to prevent physical trauma. If a soft catheter is advanced too far into the bladder, it may fold back on itself and head back into the urethra. Measuring the length of the catheter before insertion can help prevent this complication. If it is encountered, topical anesthesia and, if needed, sedation will usually allow for its removal with steady traction; however, urethral trauma is a possibility. If this or manipulation of the catheter with stylets, flushing, and passing another catheter to force the advancing end back into the bladder are unsuccessful, or the catheter has actually become knotted, surgery is indicated.

138.5 CATHETER TYPES

138.5.1 Materials

Urinary catheters are made from a variety of materials that affect stiffness, urethral reactivity, and resistance to bacterial swarming and biofilm formation. Ideally a catheter is soft for patient comfort and to limit urethral trauma, has minimal reactivity, and has resistance to biofilm formation, decreasing the potential for catheter-associated UTI. The following materials are listed in order of decreasing urethral reactivity, increasing biofilm resistance and, hence, increasing order of suitability for long-term indwelling catheterization: plastic, red rubber, latex, siliconized elastomer or Teflon-coated latex, hydrogel-coated latex, and pure silicone. Diffusion from silicone balloons has been reported, resulting in balloon deflation.[11]

138.5.2 Size

Urinary catheter size is expressed in diameter times length. The diameter units are designated using the French scale (Fr) which, when divided by 3, is the outside diameter of the catheter in millimeters; a 12 Fr catheter would have an outside diameter of 4 millimeters. The appropriate size catheter is dependent on the patient's size and sex. Cats generally need a 3.5 to 5 Fr, female dogs 3.5 to 14 Fr, and male dogs 3.5 to 10 Fr. Males require a longer catheter than females, and some catheters may be too short to reach the bladder in some males. Catheters should be measured before insertion to ensure adequate length in males.

138.6 FOLEY

Balloon-tipped catheters (with a distal port) are referred to as *Foley catheters,* named after their inventor, Dr. Frederic Foley, in 1934. Foley catheters are now available in smaller diameters and longer lengths for veterinary patients. They offer the advantage of anchoring the catheter within the bladder when a balloon near the tip is inflated. This negates the need to secure the catheter with tape and suture at the vulva or prepuce. They are ideal when an indwelling catheter is needed. They do have the potential for some unique complications related to the balloon. Overfilling the balloon may cause it to occlude the catheter lumen, and overfilling or underfilling of the balloon may deviate the tip, resulting in bladder wall contact. The balloon should be filled only with sterile water to prevent contamination due to potential permeability or rupture and, unlike saline, it will not occlude the small lumen leading to the balloon.[11]

138.7 PLACEMENT TECHNIQUE

The necessary supplies should be assembled before catheter placement, including a closed collection system if the catheter will be left indwelling (Box 138-1). Universal patient preparation includes placing the patient in lateral recumbency, clipping the hair from the preputial or vulvar area to maintain a hair-free area of at least 3 to 5 cm from the catheter insertion site, and preparing the area with a chlorhexidine scrub and tap water solution. Aseptic technique is maintained by using sterile barrier drapes and sterile gloves, along with lubricating the catheter before placement with sterile water-based (lidocaine) lubricating jelly. Before starting, measure the catheter from the urethral opening to the bladder, following the path of the urethra (maintaining sterility). Test the balloon before insertion.

Most dogs will tolerate this procedure with topical anesthetic, warmed flushing solutions, and appropriate restraint and comforting; however, many cats and some dogs will require light sedation. Benzodiazepines, through their action on peripheral skeletal muscle, may induce relaxation of the external urethral sphincter and be of benefit in the sedation cocktail.

138.7.1 Box 138-1 Supplies for Urinary Catheter Placement

138.7.1.1 General Requirements

Sterile drape for work area

Sterile barrier (patient) drape

Sterile urinary catheter

Gauze sponges

Chlorhexidine surgical scrub and water rinse

Lidocaine jelly (single use preferred)

K-Y jelly (single use preferred)

Sterile gloves

Solution of 6.25 ml chlorhexidine in 250 ml sterile water

Syringe for flushing prepuce

Syringe for Foley balloon (3 to 6 ml)

138.7.1.2 If Indwelling and Not a Foley

Suture (2-0 or 3-0 monofilament nylon)

Needle drivers, scissors, skin forceps

Tape or other securing device

138.7.1.3 Closed Collection System

Collection bag (appropriate size for animal)

If bag does not have tubing, aspiration port or male adapter for catheter

Male (referring to adapter) connector for urinary catheter

Extension tubing (1 or 2)

Three-way Luer-Lok stopcock

Infusion plug

Cable tie(s) and application gun

138.7.2 Male Dog

In males the penis is held extruded from the prepuce for the entire procedure. After cleaning the extruded penis of any gross exudate, the prepuce is flushed with 2 to 10ml of 0.05% chlorhexidine solution 5 times. With the penis still extruded, the barrier drape is applied and an appropriate-sized urinary catheter is advanced aseptically into the urethral opening and into the bladder.

138.7.3 Female Dog

The vestibule is flushed gently with 2 to 10 ml of a 0.05% chlorhexidine solution 5 times. Lidocaine jelly or solution (not to exceed 4 mg/kg) may be flushed into the area of the urethral opening a few centimeters into the vulva with a lubricated syringe (without a needle). With digital palpation of the urethral papilla by one hand, an appropriate-sized catheter is advanced under the digit into the urethral opening and into the bladder by the other hand (Figure 138-1).

Providing some rigidity to a soft catheter with a stylet or polypropylene catheter may better guide the catheter into the urethral opening. Be sure that the stylet is sterile and contained within the catheter to prevent urethral trauma. If this is unsuccessful, a disinfected laryngoscope speculum or vaginal speculum with a headlamp or other suitable light source can be used to visualize the urethral opening on the ventral floor of the vestibule-vagina interface (Figure 138-2). This can still be performed in lateral recumbency, but individual preferences may include the patient in sternal recumbency with the pelvic limbs over the edge of the table, standing, or dorsal recumbency with the pelvic limbs flexed cranially. Alternatively, an otoscope and attached cone can be used to view the urethral opening. The cone usually will not fit over the distal end of the catheter, requiring a modification of the catheter and closed collection system, or leaving the cone attached until the catheter is removed. Small dogs and puppies may require a blind technique as described below for female cats.

Figure 138-1 Urethral catheterization of a female dog. An index finger is placed over the urethral orifice to guide the catheter ventrally into the urethra. From Forrester SD, editor: *Textbook of veterinary internal medicine,* ed 6, Philadelphia, 2004, Saunders [in electronic version].

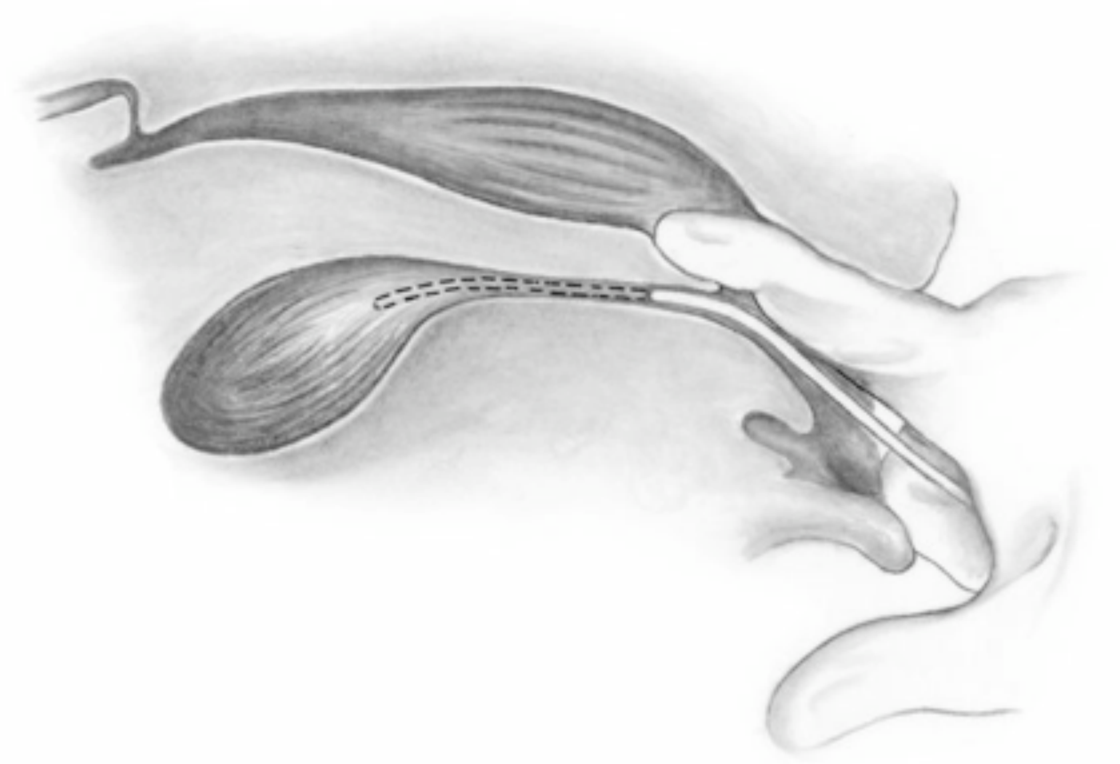
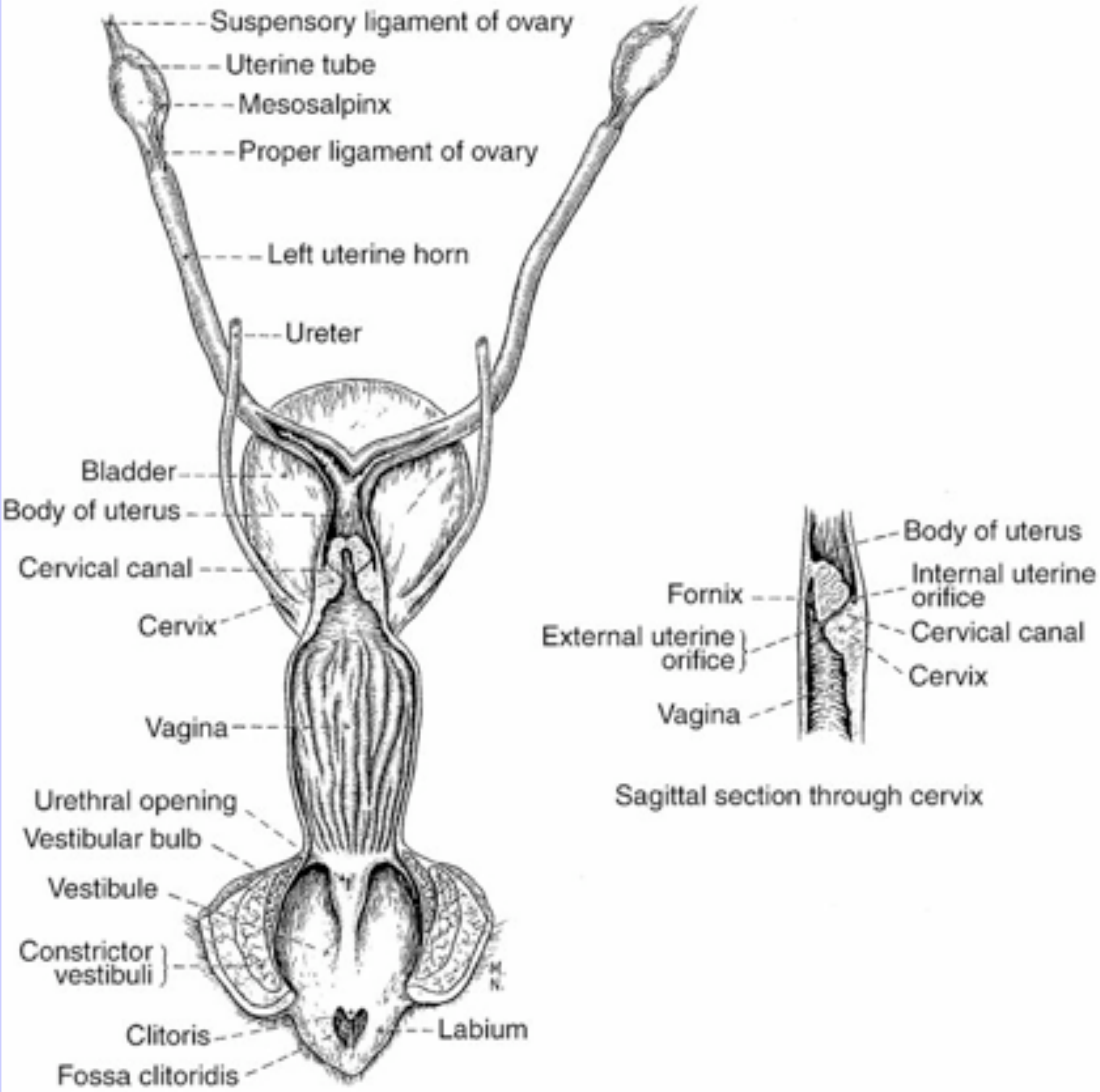


Figure 138-2 The female urethral opening. The external urethral orifice lies on the ventral floor of the vaginovestibular junction. From Evans HE: *Miller's anatomy of the dog,* ed 3, Philadelphia, 1993, Saunders.



138.7.4 Male Cat

The penis is extruded caudally with digital pressure applied to the prepuce craniodorsally. After cleaning the extruded penis of any gross exudate, the prepuce is flushed with 0.25 to 1 ml of 0.05% chlorhexidine solution 5 times. With the penis still extruded, an appropriate-sized urinary catheter (usually 3.5 to 5 Fr) is advanced into the urethral opening and into the bladder.

138.7.5 Female Cat

The vestibule is flushed with 0.5 to 2 ml of a 0.05% chlorhexidine solution 5 times. In larger cats a digital or direct-viewing method as described above for female dogs may be attempted, but usually a blind anatomic technique is employed. Directing the catheter along the midline of the ventral floor of the vestibule as it transitions to the vagina, the catheter is advanced blindly into the urethral papilla. Resistance is met at the cervix if the urethral opening is overshot, necessitating withdrawal and repeating the approach.

Urine flowing from the catheter confirms placement. If the bladder is empty, flushing and aspirating sterile saline from the catheter can support proper placement. Imaging (radiographs or ultrasonography or both) can be used if placement is still questionable. If the catheter is to be indwelling, a sterile closed collection system is connected immediately to the catheter following insertion. Cable tie(s) may be used to secure any connections and offer the advantage of visualization over taping the junctions.

138.7.6 Securing the Catheter

In the case of a Foley catheter, slightly over-advance the catheter into the bladder. Inflate the balloon with sterile saline, then retract the catheter until resistance is met. When using non-Foley type catheters, external securing systems must be used. A securing platform may be included that allows the catheter to be sutured to the skin; otherwise, a “butterfly” piece of tape can be sutured to the vulva or prepuce, adjacent to the catheter. The butterfly is an approximately 1-inch piece of ½- to 1-inch-wide tape folded upon itself, sandwiching the catheter. The tubing of the sterile collection system is then taped to the patient's tail or leg. Care should be taken to ensure that the collection system is not placing any tension on the urethral catheter or securing site.

138.8 CARE OF AN INDWELLING URINARY CATHETER

When caring for patients with indwelling urinary catheters, handwashing before and after touching each patient is a must, and wearing examination gloves as a universal precaution is good practice.

A sterile, closed collection system is the standard of care for all indwelling catheters. Reflux of urine into the bladder can be prevented by ensuring proper check valve operation of the urinary collection bag and keeping it below the level of catheter insertion. Prevent direct contact of the collection system with the floor or other grossly contaminated surface. If the urinary catheter becomes clogged with debris or blood clots, back-flushing with sterile saline may restore flow.

Every 8 hours or anytime the catheter is visibly soiled, gently clean the exposed catheter and external genitalia with chlorhexidine scrub and tap water. Rinse and flush the prepuce or vestibule 5 times with 1 to 10 ml (depending on the size of the patient) of diluted chlorhexidine solution (0.05%). Consider warming the flush solution for patient comfort, and do not introduce the solution into the urethra.

The collection bag is emptied as needed, taking care not to contaminate the drainage tube. Every effort should be made not to break the closed collection system. Samples should be obtained from the closed collection system after swabbing the sampling port with alcohol, allowing it to dry, then aspirating the desired amount with a sterile syringe and 25-gauge needle, and finally wiping the port with alcohol again. The infusion plug or closed collection system should be changed only under aseptic conditions and when the integrity of injection port is compromised.[4]

The clinician should question the need for an indwelling urinary catheter daily and remove it as soon as it is no longer needed.

138.9 SUGGESTED FURTHER READING*

1. JA Barsanti, J Blue, J Edmunds: Urinary tract infection due to indwelling bladder catheters in dogs and cats. *J Am Vet Med Assoc*. **187**, 1985, 384, *A prospective study of catheter-associated UTIs in a veterinary teaching hospital*.

2. SD Smarick, SC Haskins, J Aldrich, et al.: Incidence of catheter-associated urinary tract infection among dogs in a small animal intensive care unit. *J Am Vet Med Assoc*. **224**, 2004, 1936, *A prospective study of catheter-associated UTIs in dogs using the protocols presented in this chapter. Comparison with other veterinary studies providing review of veterinary literature of catheter-associated UTIs*.

* See the CD-ROM for a complete list of references.

139 Chapter 139 Pyometra

M. Bronwyn Crane, DVM, DACT

139.1 KEY POINTS

- Pyometra primarily affects older, intact bitches and queens.
- The pathogenesis of pyometra is hormone dependent and often preceded by cystic endometrial hyperplasia (CEH).
- Bitches have signs of endotoxemia and may or may not have vaginal discharge.
- Diagnosis is based on a combination of clinical signs, laboratory findings, abdominal radiographs, and ultrasonography.
- The recommended treatment for bitches not intended for breeding is ovariohysterectomy.
- Depending on the severity of the condition, valuable bitches intended for breeding may be treated medically. These cases have a strong likelihood of reoccurrence.

139.2 INTRODUCTION

Cystic endometrial hyperplasia (CEH)-pyometra describes a spectrum of uterine pathology that is the most common uterine disease in middle-aged and older intact bitches and queens. It is an endocrine disease occurring during diestrus, when corpora lutea are present and serum progesterone concentrations are high. Severity of the disease varies greatly and depends on its stage of progression. CEH is mostly a subclinical disease, but bitches with pyometra may be stable with mild clinical signs or near death due to toxic shock or peritonitis. Once diagnosed, CEH-pyometra may be treated by ovariohysterectomy (OHE) or medically with prostaglandin (PG) $F_{2\alpha}$ and antibiotics.

139.3 INCIDENCE

In a study of intact bitches under 10 years of age in Sweden, the 12-month incidence rate of pyometra was 2% and the average lifetime risk was 23% to 24%.[1] In colony-raised Beagle bitches, the incidence of CEH was 15.2%.[2] When medroxyprogesterone acetate was used for population control, the prevalence of pyometra increased in treated bitches to 45%, over a prevalence of only 5% in untreated bitches.[3]

139.4 PATHOGENESIS

CEH is a subclinical disease characterized by the proliferation and hypersecretion of endometrial glands, resulting in the formation of fluid-filled cysts and accumulation of glandular fluid within the uterine lumen. Alone, CEH is not associated with any signs other than infertility. CEH generally is considered the initiating stage that progresses to pyometra after uterine bacterial colonization. Pyometra is a life-threatening illness involving the accumulation of intraluminal purulent exudate within the uterus and inflammatory cell infiltration into the layers of the endometrium and myometrium. Although CEH generally precedes pyometra, the latter can occur without CEH.

CEH-pyometra typically occurs during diestrus when progesterone stimulates endometrial growth and glandular secretory activity after the uterus has been primed by estrogen. Progesterone also reduces myometrial contractility and maintains cervical closure. In addition, progesterone diminishes immune function by decreasing neutrophil chemotaxis and phagocytosis and increases endometrial bacterial adherence. Despite this, peripheral serum progesterone concentrations in bitches with pyometra are not higher than those of normal diestrual bitches.[4,5] Estrogens also have a role in the pathogenesis of CEH through the up-regulation of endometrial progesterone and estrogen receptors. Administration of estrogens followed by progesterone, or progesterone alone, will induce CEH.[6]

Bacteria gain access to the uterus via ascension during cervical dilation that occurs with estrus. Bacteria found in healthy uteri and the uteri of bitches with pyometra are representative of the normal microflora of the vagina and cervix.[7] Many bitches with pyometra also have a concurrent urinary tract infection (22% to 72%).[8] The most common bacterium isolated in cases of pyometra is *Escherichia coli.* [5] Infusion of *E. coli* isolates obtained from bitches with pyometra into the uteri of healthy bitches resulted in the development of pyometra.[9,10] Other less common bacteria isolated from cases of pyometra include *Streptococcus* spp, *Enterobacter* spp, *Proteus* spp, *Klebsiella* spp, and *Pseudomonas* spp. The mechanical irritation caused by bacteria within the endometrium is a sufficient stimulus for CEH. Any stimuli, from an embryo to a piece of silk thread,[11] will stimulate local proliferation of endometrial glands and hyperplastic changes within the endometrium.[6,12]

139.5 DIAGNOSIS

Presumptive diagnosis of CEH-pyometra is made based on the history, clinical signs, abdominal palpation of an enlarged uterus, diagnostic imaging, hematology, and biochemistry results. Differentiating CEH with mucometra from pyometra is often an important aspect of the diagnosis, because treatment recommendations may be different for valuable breeding bitches.

139.5.1 Signalment

The median age of dogs with CEH-pyometra in various studies is 8 to 9 years.[2,14] CEH is diagnosed infrequently in dogs less than 4 years old and occurs slightly more often in maiden bitches. In a retrospective study of 607
pyometra in cats, the mean age was 32 months.[13] Although there is not an established breed predisposition for 608
pyometra, studies examining the breed risk found an increased incidence in rough-coated Collies, Rottweilers, Cavalier King Charles Spaniels, and Golden Retrievers.[1,14]

139.5.2 History and Physical Examination

Most bitches and queens with pyometra have a history of recent estrus. The average interval from the onset of proestrus to diagnosis of CEH-pyometra is 35 days (range 20 to 70 days). In cats, most cases of pyometra occurred within 8 weeks of estrus and most of those queens were known to have been bred.[13] Although pyometra is considered a disorder of diestrus, it can also occur during anestrus when progesterone is at baseline concentrations. Cases that occur during anestrus may be due to the persistence of abnormal events that occurred during diestrus or a nonovarian source of progesterone. Frequently bitches with pyometra will have a history of treatment with exogenous progestins for contraception[3] or exogenous estrogens for pregnancy termination.[14]

Many cases concurrently have estrogen-secreting cystic follicles, ovarian neoplasia, or a history of prolonged estrus.

The clinical signs of pyometra include vaginal discharge (80%), fever (47%), polydipsia, polyuria, and vomition.[15] Other signs include lethargy, anorexia, dehydration, tachycardia, tachypnea, and pale or hyperemic mucous membranes. Abdominal palpation may elicit pain or reveal a large tubular structure. Uterine exudate in the form of vaginal discharge may be purulent, mucoid, or hemorrhagic. Pyometras are further classified as open cervix or closed cervix, based on the presence of vaginal discharge. Cytology of the cranial vagina will often reveal degenerate neutrophils and bacteria. Before obtaining the cytology specimen, the cranial vagina should be swabbed using a guarded swab for culture and antibiotic sensitivity testing. A vaginal speculum examination is also warranted to rule out a vaginal abnormality or foreign body as the source of vulvar discharge. Advanced cases of pyometra may arrive in decompensatory septic shock with hypotension. Signs that are more likely to be present in cases of pyometra than in CEH include polyuria and polydipsia, lethargy, and vomiting or inappetence.[16] The more severesigns associated with pyometra are due to the effects of bacterial toxins.

Clinical signs observed in queens with pyometra include vaginal discharge, anorexia, lethargy, weight loss, unkempt appearance, and polyuria and polydipsia.[13] A palpably enlarged uterus is a more common physical examination finding in cats than dogs, perhaps a result of the pliability of a cat's abdomen.

139.5.3 Diagnostic Imaging

Abdominal radiography should be performed and radiographs examined for uteromegaly. Uterine enlargement can be recognized by the presence of a fluid-filled convoluted or tubular structure between the bladder and the colon. Other potential conditions to rule out include pregnancy less than 42 days (more than 42 days after the leuteinizing hormone surge, fetal skeletons should be visible), mucometra, hydrometra, CEH, and uterine neoplasia. If the cervix is open and the uterus is draining, uteromegaly may not be present. If abdominal radiographs reveal a generalized loss of detail, it is possible that uterine rupture has already occurred.

Ultrasonography can be used to examine for uteromegaly and is particularly useful because it can be used to evaluate endometrial integrity, uterine wall thickness, uterine distention, and cystic endometrial glands. Ultrasonography can be used to differentiate pregnancy (>28 days) and neoplasia from pyometra. In cases of CEH without pyometra, endometrial glands are increased in size and number, appearing as 1- to 2-mm anechoic areas within the endometrium.[15]

139.5.4 Laboratory Findings

Neutrophilia is a common hematologic finding, ranging from 15,000 to 60,000 cells/ml. Patients with pyometra often have an increased percentage of band neutrophils. They often have an anemia of chronic disease (70% of cases)[8] that is characterized as nonregenerative, normochromic, and normocytic, and may be due to red blood cell diapedesis into the uterus or toxic suppression of erythropoiesis. Hyperproteinemia and hyperglobulinemia occur secondary to dehydration and antigenic stimulation. Hypoalbuminemia is another common finding[16] and may be due to sepsis.[8]

Approximately 12% to 37% of bitches with pyometra will have elevated creatinine and blood urea nitrogen levels.[8] Azotemia may be due to dehydration (prerenal) or reversible renal tubular damage. *E. coli* lipopolysaccharide (LPS) endotoxin causes insensitivity to antidiuretic hormone at the distal convoluted tubules and collecting ducts, which impairs concentrating ability and results in isosthenuria or hyposthenuria. This is usually reversible, but a poor prognosis is indicated if the blood urea nitrogen level is greater than 60 mg/dl. Cytotoxic necrotizing factor–positive *E. coli* also causes reversible hepatocellular damage or hypoxia due to dehydration resulting in increased aspartate aminotransferase, alkaline phosphatase, and alanine amino transferase.

When fluid in the uterus is detected, pyometra may be differentiated from CEH with mucometra by measuring percentage of band neutrophils, alkaline phosphatase, C-reactive protein (an inflammatory marker used in human medicine), or circulating prostaglandin-F metabolites (PGFM). The percentage of band neutrophils is the most sensitive single parameter for differentiating pyometra (>19.9% band neutrophils is 94.2% sensitive and 70% specific).[16] Mean alkaline phosphatase in bitches with pyometra (362 IU/L) was significantly higher than in bitches with CEH (133 IU/L) and control dogs (81 UI/L).[16] Concentrations of PGFM of 3054 pmol/L or greater indicate a 95% probability of pyometra.[17] Combining PGFM results with percentage of band neutrophils increases the sensitivity of differentiating pyometra from mucometra to 100%.[17] Bitches with more than 19.9% band neutrophils and more than 260.2 mg/L C-reactive protein had a 95% probability of having pyometra versus CEH.[16] However, neither PGFM nor canine C-reactive protein determination is readily available at most clinics.

139.6 TREATMENT

The decision to treat a bitch or queen surgically or medically will depend on the severity of clinical and laboratory findings and intended purpose of the animal. The ideal treatment for any case of pyometra is OHE. If the patient is a valuable breeding bitch and only mildly affected, then medical treatment is an option. If medical treatment does 608
not result in significant improvement within 48 hours or the condition of the patient deteriorates, then OHE should 609
be performed as soon as possible.

139.6.1 Stabilizing the Patient

It is imperative that the patient be appropriately and rapidly stabilized before surgical or medical management. Fluid therapy should be initiated to correct shock, hypoglycemia, electrolyte, and acid-base abnormalities if present (see Chapters 59, 65, and 107, Acid-Base Disturbances, Shock Fluids, and Fluid Challenge, and Septic Shock, respectively).

The patient should be started on broad-spectrum antibiotics that are effective against gram-negative pathogens until culture and sensitivity results are available. Because approximately 60% to 70% of cases are infected with *E. coli,*[5,18] antibiotic therapy should initially target this organism. Preferred antibiotics for pyometra include amoxicillin, amoxicillin-clavulanate, enrofloxacin, gentamicin, streptomycin, sulfamethoxazole, tetracycline, and trimethoprim. It is important to be cautious when using aminoglycoside antibiotics in animals with known renal dysfunction because of the risk of further renal damage. A study examining antimicrobial resistance among *E. coli* strains isolated from naturally occurring pyometra cases found minimal resistance (≤10%) to the commonly used antibiotics listed above.[18] Antibiotic therapy should be continued for at least 10 days in surgical cases[8] or 30 days in medically treated cases.[19]

Endotoxemia is present in pyometra because of the toxic effects of LPS released from bacteria. LPS may reach toxic or lethal levels of 0.7 to 1 ng/ml in bitches with pyometra.[20] Antibiotics can increase the concentration of LPS up to 2000-fold and potentially worsen the signs of endotoxemia. To augment treatment of endotoxemia, dogs can be given polyvalent equine antiendotoxin hyperimmune plasma (anti-LPS) at a dose of 0.5 mg/kg SC when surgery can be delayed 24 hours, or diluted in 100 to 300 ml lactated Ringer's solution and infused intravenously when surgery must be performed immediately.[20] No side effects have been observed in one study using this treatment, but it is likely that antibodies will be formed against the foreign proteins found in equine plasma, especially if repetitive treatments are required.

Progesterone receptor antagonists such as aglepristone (RU 534) can be used to convert a closed-cervix pyometra into an open-cervix pyometra. Aglepristone competes for uterine receptors at a fixating rate three-fold that of progesterone[21] and has virtually no reported side effects. When aglepristone was administered on days 1 and 2 after diagnosis, the mean time to cervical opening was 25.1 hours after the first injection (range 4 to 48 hours).[22] Cervical opening was associated with evacuation of large volumes of purulent exudate and an immediate improvement in general condition, with an increase in appetite.[22] Unfortunately, aglepristone is not commercially available in the United States or Canada but is marketed for veterinary use in Europe and other countries as Alizine and is produced by Virbac. It can also be used for medical management of pyometra and will be discussed later.

139.6.2 Surgical Management

OHE is the treatment of choice for bitches and queens with pyometra. Surgery should be performed as soon as they are stable and surgical risk is minimized. Depending on the condition of the patient, surgical outcome may be improved if surgery is delayed for 24 hours while the patient receives fluid therapy, antibiotics and, if available, anti-LPS plasma and aglepristone.[23]

If uterine rupture is evident at the time of surgery or peritonitis is present, the abdomen should be lavaged with copious amounts of warm saline, and management as an open abdomen may be indicated[23] (see Chapter 133, Peritonitis). Cystocentesis should be performed for urine culture before the abdomen is closed, because a high percentage of animals with pyometra also have a urinary tract infection. Following surgery, patients have a 92% survival rate, with the most common complication being peritonitis.[8]

139.6.3 Medical Management

For less severe cases of pyometra in animals intended for breeding, patients can be treated medically with combinations $PGF_{2\alpha}$ or $PGF_{2\alpha}$ analogs, progesterone receptor antagonists, and dopamine agonists. Additional supportive therapy, such as systemic antibiotics, intravenous fluid therapy, and anti-LPS plasma (if available), should be administered in all cases of pyometra. The goal of medical management is to improve the general condition of the animal, remove the source of progesterone by inducing luteolysis, stimulate uterine contractions to aid evacuation, and eliminate the infection. Various protocols for the medical management of pyometra are outlined in Table 139-1; it is important to note that recovery rate in these studies will be strongly influenced by case selection.

$PGF_{2\alpha}$ causes myometrial contractility, which expels the luminal contents. It also causes luteolysis, which decreases progesterone concentrations. Side effects of $PGF_{2\alpha}$ are associated with the dosage and include panting, salivation, anxiety, vomiting, diarrhea, urination, abdominal contractions, and ataxia within 15 minutes of administration. Additional side effects of $PGF_{2\alpha}$ treatment in queens that were not observed in dogs included vocalization, grooming, kneading, mydriasis, and lordosis.[13] Side effects may last for up to 120 minutes. Tolerance, in the form of fewer side effects, develops after repeated treatments. $PGF_{2\alpha}$ analogs, such as cloprostenol, are longer acting and more potent than natural $PGF_{2\alpha}$. They have the advantage of less-frequent administration due to their prolonged period of effectiveness. Less severe side effects are observed with cloprostenol, and dosages of 1 μg/kg have been associated with mild nausea, diarrhea, and vomiting in 31% to 55% of patients.[24,25]

Medically managed patients with pyometra should be hospitalized because of the frequent side effects, potential toxicity, and frequency of treatments. Fewer side effects can be achieved by using protocols with lower and more frequent prostaglandin doses,[25] intravaginal administration of prostaglandin,[26] combining prostaglandin with other agents such as antiprogestins[22] or dopamine agonists,[24] administering prostaglandin 1 to 2 hours from feeding, and walking the patient immediately afterward for 20 to 40 minutes. A low-dose prostaglandin protocol, such as outlined in Table 139-1, is highly effective and is associated with minimal side effects, and protocols using high dosages of $PGF_{2\alpha}$ with infrequent treatment schedules are associated with the most severe side effects. Sensitivity of the patient to $PGF_{2\alpha}$ can be assessed by beginning with a low dose and progressing to a higher dose if it is well tolerated. It is important to remember that the therapeutic index for $PGF_{2\alpha}$ in dogs is 609 610 narrow, with a lethal dose of 5.13 mg/kg for dinoprost (natural $PGF_{2\alpha}$). Although various prostaglandin protocols are published with finite treatment periods, it is best to monitor uterine diameter ultrasonographically and continue treatment until uterine diameter returns to normal and until a purulent vulvar discharge is no longer present (up to 2 to 3 weeks).[27]

Table 139-1 Protocols for the Medical Management of Pyometra in Bitches, Used in Addition to Antibiotic and Fluid Therapy

Protocol	Drug and Dosage	Frequency	Recovery Rate	Reference
Low $PGF_{2\alpha}$	Dinoprost 0.02 to 0.1 mg/kg SC	q2-4h until uterine evacuation or luteolysis	75% (9 of 12)	27, 25
Medium $PGF_{2\alpha}$	Dinoprost 0.1 to 0.25 mg/kg SC	q24h	Not reported	8, 19
High $PGF_{2\alpha}$	Dinoprost 0.25 to 0.5 mg/kg SC	q24h for 3 days	100% (10 of 10)	29
$PGF_{2\alpha}$ in queens	0.1 mg/kg SC	q12-24h for 3 to 5 days	95.2% (20 of 21)	13
Intravaginal $PGF_{2\alpha}$	Dinoprost 0.15 mg/kg intravaginally at 0.3 ml/kg	q12h for 3 to 12 days	81.8% (9 of 11)	26
$PGF_{2\alpha}$ analog	Cloprostenol 1 to 5 μg/kg SC	q12-24h	Not reported	27, 19
$PGF_{2\alpha}$ analog + dopamine agonist	Cloprostenol 1 μg/kg SC Cabergoline 5 μg/kg PO	Both q24h for 7 days, cloprostenol q24h for up to 14 days	83% (24 of 29)	24
Antiprogestin	Aglepristone 10 mg/kg SC	Once on days 1, 2, 8, 14, and 28*	45% (9 of 20) by day 28 60% (12 of 20) by day 90	22
Antiprogestin + $PGF_{2\alpha}$ analog	Aglepristone 10 mg/kg SC	Aglepristone once on days 1, 3, 8, and 15*	100% (8 of 8)	21
	Cloprostenol 1 μg/kg SC	Cloprostenol once on days 3 and 8		
	Aglepristone 10 mg/kg SC	Aglepristone once on days 1, 3, 8, and 15*	100% (7 of 7)	21
	Cloprostenol 1 μg/kg SC	Cloprostenol once on days 3, 5, 8, 10, 12, and 15*		
	Aglepristone 10 mg/kg SC	Aglepristone once on days 1, 2, 8, 14, and 28*	72% (23 of 32) by day 28	2
	Cloprostenol 1 μg/kg SC	Cloprostenol once on days 3, 4, 5, 6, and 7	84% (27 of 32) by day 90	

PGF, Prostaglandin F; *PO,* per os; *SC,* subcutaneous.

Progesterone receptor antagonists or antiprogestins, such as aglepristone, result in better recovery rates when they are used in conjunction with prostaglandins (see Table 139-1). Interestingly, a positive effect of aglepristone alone has also been found in bitches with basal progesterone concentrations[21] and may be due to an increased sensitivity of receptors. Aglepristone can also be used to prevent reoccurrence of pyometra in treated bitches that are not inseminated at a subsequent estrus.[28] Aglepristone is unique in that it offers a safe method of converting a closed pyometra into an open pyometra for medical management.[22] Because of the delay (4 to 48 hours) before the cervix opens, medical treatment of a closed pyometra should not be attempted in bitches with compromised liver or kidney function. Prostaglandin therapy may be successful in patients with closed pyometras, but is generally not recommended because of the risk of uterine rupture or expulsion of uterine contents from the oviducts into the peritoneal cavity.[28]

Dopamine agonists, such as cabergoline, cause luteolysis by reducing prolactin concentrations. Prolactin is a major source of luteotropic support in the bitch. Dopamine agonists should be used in combination with prostaglandin (see Table 139-1), because together they result in more complete luteolysis. Meanwhile, prostaglandin exerts a uterotonic effect. The combined use of these drugs allows a lower dose of prostaglandin and reduces the side effects.

Once recovered, the bitch should be reevaluated between 10 and 20 days after her last treatment and the need for additional treatment determined at that time.[28] The recurrence rate of pyometra within 1 to 2 years in medically managed cases is between 20% and 77%.[24,29] A slightly lower recurrence rate (3 of 21) was observed in queens treated with $PGF_{2\alpha}$.[13] To prevent reoccurrence during the next cycle, the bitch should undergo timing for her leuteinizing hormone surge and be bred to a male with known fertility during her most fertile period. Prophylactic antibiotics may be given during proestrus and estrus. If the owners choose not to breed the bitch, antibiotics and aglepristone[27] can be given to prevent recurrence. Approximately 40% to 90% of bitches whelp a normal litter following medical management.[19,29] Young bitches or those developing pyometra as a result of exogenous estrogen or progesterone therapy are more likely to maintain a pregnancy following treatment.

* Treatment was continued beyond day 8 only if necessary.

139.7 UTERINE STUMP PYOMETRA

Uterine stump pyometra has a pathogenesis similar to that of pyometra, with the exception that the patient was previously believed to have had the uterus and ovaries completely removed. In patients with a uterine stump pyometra, remnants of ovarian tissue with a variable amount of uterine tissue have been left behind following OHE.[19] The clinical signs are similar to those of CEH-pyometra and include vulvar discharge, depression, and anorexia. Diagnosis is made by retrograde vaginography and ultrasonography that reveal single or multiple fluid-filled areas adjacent to the bladder. Other methods of diagnosis include abdominal palpation, laboratory evaluation, radiography, and exploratory laparotomy. Management involves surgical resection of all remaining uterine and ovarian tissue. 610 611

139.8 SUGGESTED FURTHER READING*

E Bigliardi, E Parmigiani, S Cavirani, et al.: Ultrasonography and cystic hyperplasia–pyometra complex in the bitch. *Reprod Domest Anim*. **39**, 2004, 136, *Study that evaluated ultrasonography as a tool for diagnosing CEH-pyometra in naturally occurring cases and compared results with clinical signs and laboratory findings.*

LA Jutkowitz: Reproductive emergencies. *Vet Clin North Am Small Anim Pract*. **35**, 2005, 397, *An excellent review article that gives an appropriate amount of detail for a clinician handling an emergency situation.*

DE Noakes, GK Dhaliwal, GCW England: Cystic endometrial hyperplasia–pyometra in dogs: a review of the causes and pathogenesis. *J Reprod Fertil Suppl*. **57**, 2001, 395, *An excellent review of the pathogenesis of CEH-pyometra*.

* See the CD-ROM for a complete list of references

140 Chapter 140 Dystocia and Obstetric Crises

Michelle Kutzler, DVM, PhD, DACT

140.1 KEY POINTS

- Knowledge of actual length of gestation and timing of normal events during parturition are critical when managing dystocia.
- Primary uterine inertia is the most common cause of dystocia in dogs and cats.
- Diagnosis of dystocia can be made from the history and physical signs. However, diagnosing the cause of dystocia may require biochemical testing, vaginal palpation, radiographic and/or ultrasonographic imaging, and uterine contractility monitoring.
- If obstructive causes of dystocia have been ruled out, oxytocin administration may be employed provided that fetal heart rates are normal. Subcutaneous or intramuscular oxytocin (0.25 to 2.0 IU per bitch or queen initially; maximum administered dose of 4 IU) induces uterine contractility lasting for 30 to 90 minutes.
- Sequelae of dystocia include neonatal and maternal mortality, retained placenta, uterine prolapse, and perineal-vaginal fistula formation.

140.2 NORMAL PARTURITION

Knowledge of actual length of gestation is critical when managing dystocia. Female cats are seasonally polyestrous, with ovulation occurring 24 to 48 hours after breeding. The interval from ovulation to parturition is 63 to 65 days.[1] The apparent length of gestation in the dog ranges from 58 to 72 days from the first of multiple breedings because of the variability in the onset of estrous behavior, prolonged viability of sperm in the uterus, and prolonged life span of the oocytes. Predicting parturition date in the bitch is straightforward if ovulation timing has been performed, because length of gestation is 56 to 58 days from the onset of cytologic diestrus or 64 to 66 days from the surge in luteinizing hormone. The most definite indication of impending parturition is a sudden drop in body temperature that occurs with prepartum luteolysis (decline in progesterone). Rectal temperature decreases by at least 2° F (1° C) 12 to 24 hours before the onset of parturition. However, the hypothermia is transient and body temperature rises during parturition, remaining slightly above normal for several days.

The first stage of labor is characterized by intermittent uterine contractions associated with cervical dilation, vaginal relaxation, and behavioral changes (restlessness, panting, and nesting). In the bitch, the first stage of labor lasts 6 to 12 hours. Uterine contractions that occur during this stage are not visible externally and are not accompanied by voluntary abdominal contractions.

The second stage of labor is characterized by intensified uterine contractions accompanied by voluntary abdominal efforts, resulting in fetal expulsion. In the bitch, the second stage of labor lasts for 3 to 12 hours and, in rare cases, up to 24 hours depending on litter size and without obvious complications.[2–4] Canine litter size ranges from 1 to 23 pups, with mean litter sizes ranging from 4 to 8 depending on breed (up to 10 pups in Bloodhounds and fewer than 3 pups in Pekingese and Pomeranians).[5] Average feline litter size is 3 to 4 kittens.[1]

Approximately 60% of canine and feline fetuses are delivered in cranial presentation, with the remainder delivered in caudal presentation. Fetuses typically are covered by the amnion at the time of delivery.[3] Delivery is initiated from the uterine horn carrying the most fetuses unless they are evenly distributed between the uterine horns; then they are delivered alternately from the two horns.[3] Expulsion of the first fetus may take up to an hour,[2] usually within 15 minutes from the onset of forceful straining.[3] Survival of the first fetus after initiation of second stage labor is estimated to be 6 to 8 hours, but little is known about canine and feline fetal intrapartum survival if dystocia occurs.

The interval between delivery of individual fetuses ranges from 5 minutes to 2 hours.[3,4,6] When more than 2 hours elapses between consecutive births, fetal survival is thought to be endangered. Intrapartum uterine contractions occur mainly at the level of the uterus around the fetus closest to the cervix, which may explain the birth of normal fetuses even with prolonged intervals between delivery. It is important to note that stressed bitches can postpone the delivery of pups for up to 1 day without complications,[7] although such postponement generally applies to onset of parturition rather than a prolongation of the interpup interval.[8] During dystocia, excessive and prolonged straining may result in premature placental separation and fetal mortality. However, in the absence of straining, the risk of intrapartum fetal death may not be increased.[8]

Throughout and following parturition, dark green uterine discharge (uteroverdin) originating from the uteroplacental marginal hematomas is present in bitches. The third stage of labor is characterized by placental expulsion and uterine involution. Placentas are delivered 5 to 10 minutes following delivery of the fetuses. Two to three fetuses may be delivered before their placentas are passed.[3] The physiology of placental detachment is not well understood in cats and dogs. However, placental aging and detachment can occur even in the presence of high progesterone concentrations, suggesting that the placenta has a predetermined life span that cannot be prolonged with progestin supplementation.[9]

140.3 ETIOLOGY AND INCIDENCE

Dystocia comes from the Greek *dys* (difficult) and *tokos* (birth). Dystocia can be classified as functional or obstructive. Functional dystocia usually is termed *inertia* and can be classified as primary or secondary. Primary uterine inertia is the most common cause of dystocia in dogs and cats, with a reported incidence of up to 91% of cases.[4,10,11] In primary uterine inertia, the myometrium produces weak, infrequent contractions resulting in a failure to deliver the fetuses. Primary uterine inertia can be further classified as complete or partial.[12] In complete primary inertia, second stage labor does not start; whereas in partial primary inertia, second-stage labor starts but labor ends prematurely in the absence of obstructive causes.

Secondary uterine inertia occurs following a prolonged second stage of labor and may be associated with obstructive dystocia. Obstructive dystocia may result from relative or absolute fetal oversize. Absolute fetal oversize refers to a fetus that is too large to pass along a maternal birth canal that is of normal dimensions. Relative fetal oversize refers to a fetus of normal size that cannot pass along the maternal birth canal because the latter is abnormally small or restricted in some way. Relative fetal oversize is equivalent to a maternal obstructive dystocia. Known and speculated etiologies for both functional and obstructive dystocia are listed in Box 140-1.

Certain canine and feline breeds are overrepresented in cases of dystocia, with the incidence approaching 100% in some breeds. Bulldogs and other brachycephalic breeds, Cocker Spaniels, Dachshunds, Terrier breeds (e.g., Scottish, Aberdeen, Border), and Welsh Corgis have a higher incidence of dystocia than other breeds.[2] Dystocia is reportedly rare in the Greyhound.[13] The overall incidence of canine dystocia is approximately 5% of all pregnancies.[3] The overall incidence of feline dystocia irrespective of breed is 5% to 8%.[14] However, the incidence of dystocia is 18% to 20% in British Short-Haired, Cornish Rex, Devon Rex, Persian, and Siamese breeds.[14] In addition, the relative risk of dystocia is higher in dolichocephalic and brachycephalic breeds compared with mesocephalics (Abyssinian, Burmese, and Manx).[14]

140.4 DIAGNOSIS

The standard approach to labor management in small animal patients involves subjective client monitoring of behavior, progression of whelping, and the physical condition of the neonates. Dystocia can be diagnosed when (1) a definite cause of dystocia is apparent (e.g., fetus is presented at vulva); (2) constant, severe, unproductive labor fails to result in delivery of a fetus within 20 to 30 minutes; (3) weak, infrequent labor fails to be productive within 2 to 3 hours; (4) more than 4 hours has elapsed since the delivery of the previous fetus and there has been no evidence of labor; (5) signs of toxemia are present when parturition should be occurring; or (6) abnormal vaginal discharge (e.g., blood, pus, uteroverdine before the delivery of any fetuses) is present. Uterine torsion or rupture may occur near the end of gestation, and may present with the dam in abdominal pain or shock.[15] Diagnosis of uterine torsion or rupture may not be possible without a laparotomy and corrective hysterectomy or hysterotomy (if the condition occurs at term).[15]

Minimum baseline hematologic and biochemical testing in cases of dystocia include a complete blood count, creatinine (or urea nitrogen), glucose, calcium, and total protein, and possibly a coagulation panel.[16] The hematocrit falls below 35% during the last 2 weeks of pregnancy from hemodilution, a result of increased plasma volume rather than absolute anemia. There is also a decrease in hemoglobin with an increase in sedimentation rate. However, the total and differential leukocyte counts and total protein remain unchanged during pregnancy. Plasma fibrinogen levels increase significantly before parturition,[17] as do the biologic activities of factors VII, IX, and XI.[18] In addition, insensitivity to insulin, but not glucagon, develops during the last half of pregnancy.[19] Other physiologic changes that occur during normal gestation include: (1) increased cardiac output with increased systemic and pulmonary vascular resistance and increased venous distensibility,[20] (2) increased minute ventilation and oxygen consumption with decreased functional residual capacity and anesthetic requirement,[21] and (3) delayed gastric emptying.

The vagina should be examined digitally for evidence of abnormalities or obstructed fetuses. Digital palpation of the vagina may reveal a softening cranial vaginal wall compatible with the second stage of parturition. However, it is not possible to assess cervical dilation in bitches by vaginal digital examination because of the vaginal length. Vaginoscopy with a rigid cystourethroscope used for transcervical intrauterine insemination can be used to determine the status of the cervix. It is important to note that digital exploration of the vagina may result in release of endogenous oxytocin release and stimulate uterine contractility.

Abdominal imaging is extremely important in determining the cause of dystocia. Radiography is useful for confirming pregnancy, as well as determining the number of fetuses. Radiographs of fetal skeletons, sufficiently distinct for an unequivocal diagnosis, can be obtained 17 to 20 days before parturition.[22,23] Radiographs may also be used to detect fetal death. During the final stages of intrauterine development, fetal death is evidenced by 612
intravascular fetal or extra fetal intrauterine gas formation, overlap of cranial bones, and abnormal fetal posture.[24] 613
In addition, radiographic pelvimetry may be used to predict a disposition for dystocia in individual bitches as well as for selection of breeding animals, because some terrier breeds (Boston and Scottish) have an increased incidence

of dorsoventral flattening of the pelvic canal.[25] However, uterine inertia, the most common cause of dystocia, can not be diagnosed radiographically.[26]

140.4.1 Box 140-1 Causes of Functional and Obstructive Dystocia in Dogs and Cats

140.4.1.1 Primary Uterine Inertia

Age

Absence of fetal fluid

Dietary deficiencies

- Hypocalcemia
- Hypoglycemia
- Hypomagnesemia

Environmental disturbance

- Stressed
- Unfamiliar surroundings

Large litter size

- Excessive uterine distention
- Overstretching

Myometrial defect

- Hereditary
- Infection

Obesity

- Fatty myometrial infiltration

Oxytocin deficiency

Small litter size

  - Insufficient fetal cortisol

Systemic illness

140.4.1.2 Secondary Uterine Inertia

Diaphragmatic rupture

Excessive pain

Muscle fatigue

Obstructive dystocia

Perforated trachea

Uterine rupture

140.4.1.3 Maternal Obstructive Dystocia

Aberrant round ligaments encircling the uterine horn

Ectopic pregnancy

  - Extrauterine mummified fetus

Inadequate cervical dilation

  - Fibrosis
  - Congenital defect

Inadequate pelvis size

  - Breed
  - Congenital defect
  - Fracture
  - Immaturity

- Neoplasia

Inguinal herniation of the uterus

Uterine torsion

Vaginal abnormality

- Congenital defect
- Cyst
- Neoplasia
- Prolapse
- Vaginovestibular stenosis

Vulvar abnormality

140.4.1.4 Fetal Obstructive Dystocia

Abnormal fetal position

- Ventral
- Lateral

Abnormal fetal posture

- Cranial-to-limb flexion
  - Carpal
  - Elbow
  - Shoulder
- Head flexion
  - Lateral
  - Upward
  - Downward
- Caudal

  - Hock flexion
  - Hip flexion

Abnormal fetal presentation

- Transverse
- Bicornual

Absolute fetal oversize

Developmental defect

- Anasarca
- Conjoined twins
- Hydrocephalus
- Hydrops amnion
- Fetal monsters

Fetal death

Antemortem fetal viability can be assessed by monitoring fetal heart rate.[27] Ideally, fetal heart rates should be assessed a minimum of once before labor and then every 1 to 2 hours (or more frequently) during labor. Normal canine and feline fetuses at term have heart rates at least twice the maternal rate.[6] Normal transient accelerations occur with fetal movement (e.g., swallowing, hiccups, body or limb movements).[27] Fetal distress is indicated by sustained deceleration of the heart rates.[6] Decelerations associated only with uterine contractions suggest an obstructive cause for dystocia.[6] Fetal death is recognized by absence of heartbeats. Fetal heart rates should always be assessed before administering any medication that may affect uterine contractility or blood flow.

Unfortunately, information concerning actual uterine activity usually is not obtained when managing canine and feline obstetric crises. Uterine monitoring systems consisting of a tocodynamometer, a recorder, and a modem are commercially available (Whelp Wise Service, Veterinary Perinatal Specialties, Wheat Ridge, CO) to detect changes in intrauterine and intraamniotic pressures in both dogs and cats.[28] The tocodynamometer is strapped over a lightly clipped area of the caudolateral abdomen with an elasticized strap, and the recorder is worn in a small backpack during monitoring.[28] The monitoring equipment is well tolerated by dams.[28]

140.5

TREATMENT

Dehydration, hypoglycemia, and hypocalcemia have all been reported as factors contributing to dystocia, predominately uterine inertia. Because these topics are covered in greater detail in other chapters of this text, minimal information will be reported here. If present, dehydration should be corrected with intravenous balanced electrolyte solutions such as lactated Ringer's. Hypoglycemia with ketonemia has been reported in several pregnant bitches with a rapid response to treatment with a 20% intravenous glucose solution. Eclampsia (puerperal tetany) is caused by a calcium ion deficiency and usually occurs postpartum, but it may occur immediately before or during parturition.[15] Eclampsia is treated by slow intravenous administration of calcium borogluconate solution given to effect.[3] Administration of calcium borogluconate solution also increases the strength of myometrial contractions and promotes uterine involution, which may alleviate dystocia caused by primary uterine inertia and control postpartum hemorrhage, respectively.[3]

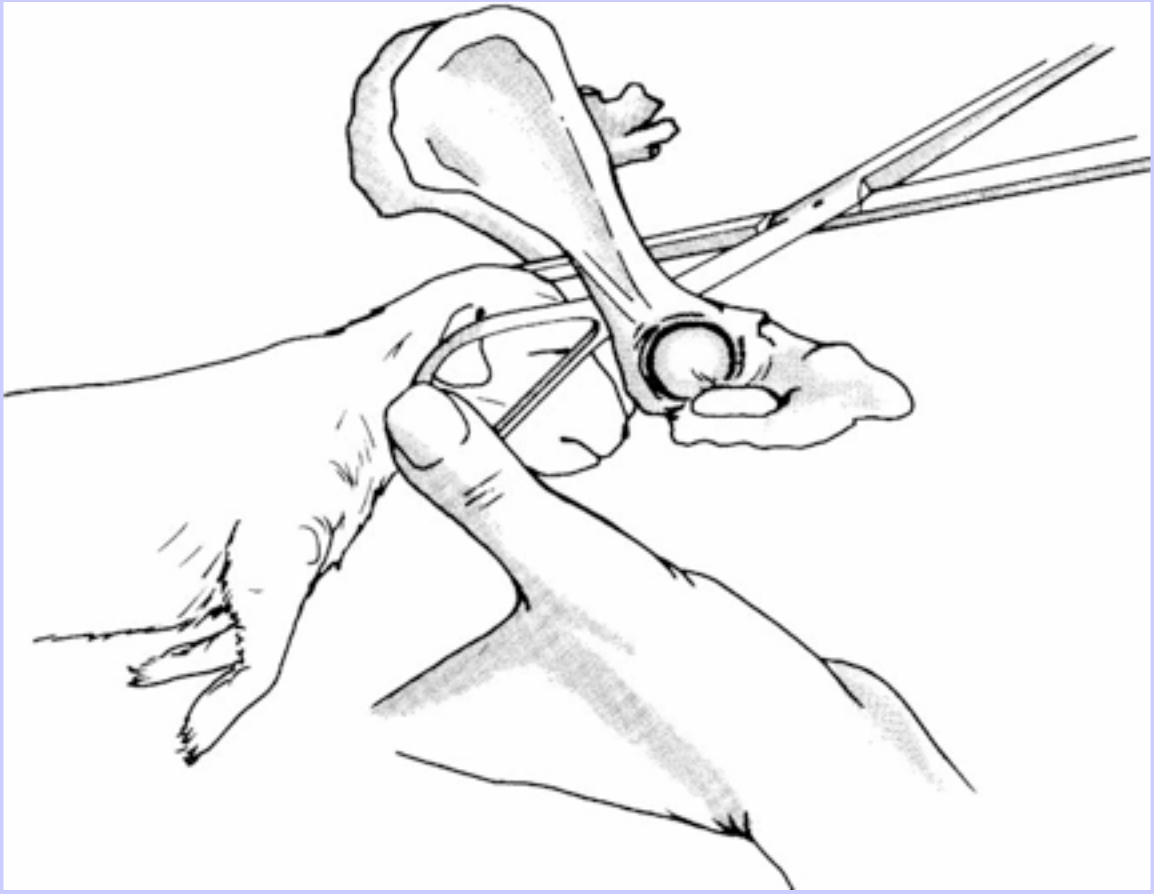
If obstructive causes of dystocia have been ruled out and primary uterine inertia is suspected, oxytocin may be administered provided that fetal heart rates are normal. Plasma oxytocin concentrations are reported to be 2 to 3 times lower in bitches with uterine inertia compared with bitches in normal labor.[29] However, 30% of bitches with uterine inertia do not respond to oxytocin, indicating a defect in or a down-regulation of the myometrial oxytocin receptor function.[8,29]

Unlike calcium that increases the strength of myometrial contractility, oxytocin increases the frequency of myometrial contraction. Subcutaneous or intramuscular oxytocin (0.25 to 2.0 IU per bitch or queen initially; maximum administered dose of 4 IU) induces uterine contractility lasting for 30 to 90 minutes. Higher dosages of oxytocin (up to 20 IU) cause tetanic, ineffective uterine contractions that compromise fetal oxygen supply by placental compression and detachment, resulting in fetal death.[12,28] However, dose-response studies indicating the critical oxytocin dosage at which placental detachment occurs are not available. Surgical intervention is advised if two injections of oxytocin administered at 30- to 60- minute intervals fail to result in a return to normal labor.[3,4]

If dystocia is due to obstruction within the caudal birth canal, vaginal extraction may be attempted when removal of the obstructive puppy may be reasonably expected to result in the normal progression of parturition or if it is the last puppy.[3] Simple digital delivery of the fetus should always be attempted initially, before obstetric instruments (e.g., Rampley sponge-holding forceps, Hobday forceps [Figure 140-1], Robert snare forceps [Figure 140-2], obstetric hook) are used.[2,3] Fetotomy[2] or episiotomy[3] can also be combined with vaginal extraction.

If the obstruction is cranial to the vagina or if the dam is ill or in shock, surgical intervention must be considered. Indications for a cesarean section include (1) primary complete uterine inertia, (2) medically unresponsive primary partial uterine inertia, (3) secondary uterine inertia, (4) relative fetal oversize, (5) absolute fetal oversize, (6) evidence of fetal distress (heart rate deceleration), and (7) maternal systemic illness. There is a wide variation in anesthetic protocols for a cesarean section, and the clinician should critically weigh risks of neonatal and maternal morbidity and mortality when selecting anesthetics.

Figure 140-1 Delivery of a puppy with retention using Hobday forceps. While the position of the fetus is fixed through the abdominal wall with the left hand, the forceps are applied to the skull with the right hand. Reprinted with permission from Arthur GH, Noakes D, Pearson H: *Veterinary reproduction and obstetrics (theriogenology),* ed 5, London, 1984, Bailliere Tindall.



140.6

SEQUELAE OF DYSTOCIA

During dystocia, the lives of both dam and fetuses are in jeopardy. The priorities for survival of the dam and the offspring should be established before beginning any treatment. These priorities will be determined by the client's wishes and the relative viability and value of the offspring and/or the dam.

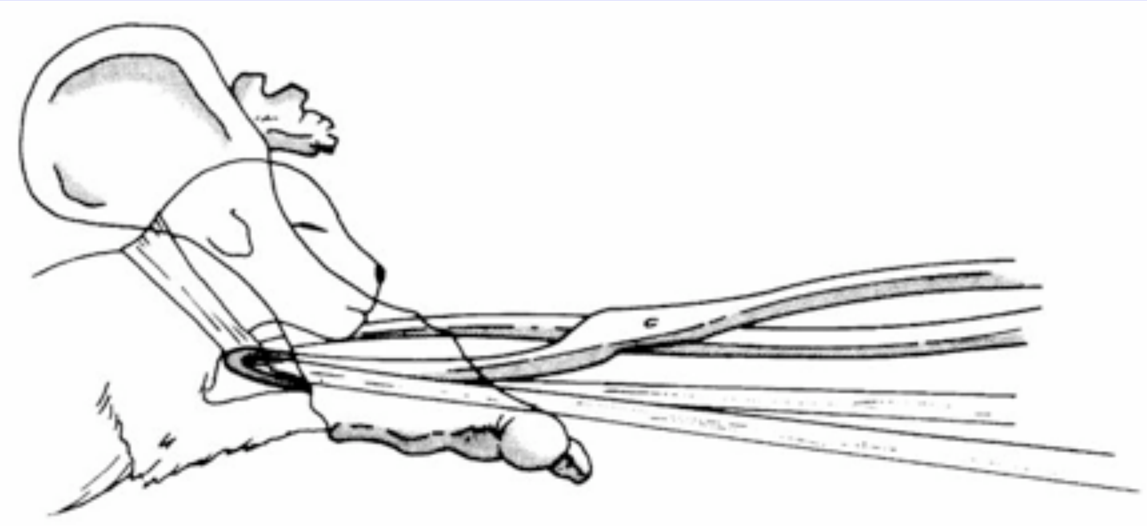
Maternal mortality can be reduced appreciably by appropriate supportive care. Calm, gentle handling is important to minimize maternal excitement and catecholamine release that can result in decreased uterine blood flow. In either spontaneous or oxytocin-induced labor, uterine contractions are accompanied by a significant decrease in uterine blood flow.[30] When myometrial contractions are tetanic and not followed by relaxation, as seen following large doses of oxytocin, uterine ischemia is severe.[30]

All forms of dystocia increase the risk of fetal death by anoxia.[3] Supplemental oxygen before and during management of dystocia is extremely desirable to help minimize the incidence of maternal and/or fetal hypoxia. Fetal mortality has been reported as high as 74% in dogs with dystocia lasting longer than 12 hours.[4] A 7.9% loss of viable neonates within the first 24 hours postpartum has been attributed to dystocia.[31]

Additional sequelae of dystocia include retained fetal membranes, uterine prolapse, and formation of a rectovaginal fistula. Fetal membrane retention inevitably is associated with uterine inertia and can lead to putrefaction and septic metritis. Diagnosis of fetal membrane retention is made when copious vaginal discharge continues beyond 12 hours postpartum along with systemic illness and detection of the membranes by abdominal palpation or ultrasonography. Medical management includes oxytocin administration with systemic antimicrobial therapy and general supportive care.

Uterine prolapse seldom is encountered in dogs and cats. One or both of the uterine horns may prolapse, with unilateral prolapse being the most common form. In the event of a unilateral uterine prolapse, fetuses may still be present in the other horn. Four techniques have been described for managing uterine prolapse in small animal patients: (1) manual reduction with immediate ovariohysterectomy, (2) ovariohysterectomy without manual reduction, (3) laparotomy with manual reduction and hysteropexy, and (4) amputation of the uterine horn.[32–34] Manual reduction can be facilitated with a plunger from a sterile 10-ml syringe and a sterile insemination tube.[34]

Figure 140-2 Robert snare forceps applied to the fetal neck. Reprinted with permission from Arthur GH, Noakes D, Pearson H: *Veterinary reproduction and obstetrics (theriogenology)*, ed 5, London, 1984, Bailliere Tindall.



In addition to retained fetal membranes and uterine prolapse, severe perineal trauma can occur if vaginal extraction is attempted. Formation of a rectovaginal fistula has been reported once following trauma that occurred during traction applied to deliver the fetuses during an obstructive dystocia.[35] The application of copious water-soluble lubrication and gentle fetal traction should minimize the risk for serious maternal injury to occur during obstetrical manipulations.

140.7 SUGGESTED FURTHER READING*

AW Darvelid, C Linde-Forsberg: Dystocia in the bitch: a retrospective study of 182 cases. *J Small Anim Pract*. **35**, 1994, 402, *A retrospective study of 182 cases of canine dystocia, with intrapartum mortality in 52.2% of litters with a total loss of 22.3% of pups. The most common cause of dystocia: primary complete uterine inertia (48.9%); small litters of one or two pups in 40% of bitches with primary complete uterine inertia*.

AP Davidson: Uterine and fetal monitoring in the bitch. *Vet Clin North Am Small Anim Pract*. **31**, 2001, 305, *A review reporting on the improvement of outcomes associated with uterine and fetal monitoring in canine obstetrics. Bitches with a history of cesarean section may be able to whelp vaginally with medical intervention based on monitoring*.

C Ekstrand, C Linde-Forsberg: Dystocia in the cat: a retrospective study of 155 cases. *J Small Anim Pract*. **35**, 1994, 459, *A retrospective study of 155 cases of feline dystocia: 67.1% of maternal origin mainly caused by uterine inertia; 29.7% of fetal origin, mainly resulting from malpresentation/malorientation, and deformities*.

CA Johnson: Disorders of pregnancy. *Vet Clin North Am Small Anim Pract*. **16**, 1986, 477, *Review of several disorders of pregnancy including: ectopic pregnancy, prolonged gestation, spontaneous abortion and embryonic death, uterine torsion, hypocalcemia, hypoglycemia, and dystocia*.

GC Van der Weyden, MA Taverne: Aspects of obstetric care in the dog. *Vet Q*. **16**(Suppl 1), 1994, 20S, *Reference that reports on treatments and side effects of treatment for prolonged gestation and primary uterine inertia*.

* See the CD-ROM for a complete list of references.

141 Chapter 141 Paraphimosis and Priapism

Mark C. Rochat, DVM, MS, DACVS

141.1 KEY POINTS

- Paraphimosis is the inability to reduce the penis into the prepuce.
- Paraphimosis can result from a number of causes and should be considered an emergency condition.
- Recurrent paraphimosis can be managed with phallopexy.
- Priapism is persistent penile erection in the absence of sexual stimulation.
- Priapism can result from many causes and should be considered an emergency condition.
- Priapism can be classified as high flow or low flow; low-flow priapism is far more common.
- Oxygen free radical scavengers may play an effective role in the management of priapism.
- Corporal aspiration and saline lavage, coupled with injection of phenylephrine, should be the first-line element of management for low-flow priapism.
- Surgical shunts or other interventions should be reserved for cases unresponsive to medical management.

141.2 PARAPHIMOSIS

Paraphimosis results when the penis cannot be ensheathed in the prepuce.[1,2] Paraphimosis is more common in dogs than cats and may be more common in young dogs. Paraphimosis can result from a number of conditions (Box 141-1). Initially, the exposed penis often appears normal but may be engorged if the paraphimosis occurs following an erection, or may be edematous due to continued environmental exposure. Continued environmental exposure and constriction results in venous congestion, mucosal drying, and further increase in penile edema.[1,3] With time, thrombosis of the penile vasculature, mucosal fissuring, and necrosis may result.

141.2.1 Box 141-1 Causes of Paraphimosis

- Coitus
- Penile entrapment by hair around the preputial orifice
- Mild phimosis
- Trauma (including fractures of the os penis)
- Neoplasia
- Pseudohermaphroditism
- Foreign bodies that encircle and constrict the penis

- Penile hematomas
- Preputial orifice inversion
- Preputial hypoplasia
- Preputial muscular weakness
- Chronic balanoposthitis

The diagnosis of paraphimosis is made by visual examination of the genitalia. Because paraphimosis is very painful in the early stages, sedation or anesthesia may be required to examine the penis and prepuce. The extent of mucosal injury and the potential for penile necrosis and urethral compromise should also be assessed.

Treatment of paraphimosis involves gentle cleaning of the penis and judicious debridement of necrotic tissue. Encircling bands of hair or other material should be removed carefully.[1] When possible, the penis is then reduced manually into the prepuce. Cooling the penis to cause vasoconstriction or applying topical agents such as lubricants or dextrose solutions may help reduce the edema and facilitate reduction.[1] Surgical enlargement of the preputial orifice may be required to achieve reduction if it cannot be accomplished manually.[2] A temporary purse-string suture placed in the skin of the preputial orifice can be inserted to maintain reduction of the penis after it has been replaced in the prepuce.

Following the initial intervention, the penis can be extruded gently on a daily basis for several days and antibiotic-steroid ointment applied to prevent adhesions between the prepuce and the penis.[1] If the urethral lumen has been compromised but the penis is otherwise viable, a Silastic urethral catheter that is smaller than the diameter of the urethral lumen should be inserted to decrease the risk of urethral occlusion secondary scar tissue.[1]

Several surgical procedures can be used to manage paraphimosis. If the penis cannot be maintained in the prepuce or the paraphimosis recurs repeatedly, phallopexy can be performed by creating a permanent adhesion between the shaft of the penis and the dorsal or dorsolateral preputial mucosa.[4] If inadequate preputial length is the cause of the paraphimosis, the prepuce can be advanced surgically. Preputial advancement usually is successful only if the length of exposed penis is limited to 1 to 2 cm.[2] If more than 1 to 2 cm of the penis is exposed, preputioplasty or partial penile amputation may be required.[2] Partial penile amputation is also the management for penile neoplasia, severe penile trauma, congenital abnormalities, and chronic paraphimosis that is unresponsive to less aggressive treatments. If the penis is necrotic, complete penile amputation with scrotal urethrostomy may be necessary.

Paraphimosis can recur, especially if it is associated with sexual behavior. Efforts to prevent recurrence, such as trimming of the preputial hair, careful inspection of the penis and prepuce after breeding, administration of progestogens, and castration, can be employed.[3]

141.3 PRIAPISM

Priapism is a persistent penile erection in the absence of sexual stimulation. The penis cannot be reduced manually into the prepuce. Priapism is a rare disorder in domestic animals. It has been reported in the dog, horse, cat, rat, and sea lion. Priapism can be confused with the late stages of paraphimosis or penile paralysis. Unlike priapism, penile paralysis results in a flaccid penis that cannot be retracted into the prepuce. Penile paralysis most commonly occurs in the horse after giving α-adrenergic blocking agents such as phenothiazine-derivative tranquilizers. Penile paralysis has not been reported in the dog.

141.3.1 Etiology and Pathophysiology

Unlike paraphimosis, which is largely initiated by physical events or structural abnormalities, priapism is initiated by alterations in the mechanisms that control penile erection. The physiology of erection is a complex and detailed subject. In the interest of brevity, the reader is directed to a review of the physiology of normal penile erection.[5]

The causes of priapism in dogs and cats are diverse (Box 141-2), and many of the exact mechanisms are unknown; however, phenothiazine-derived tranquilizers are reported to create priapism in the horse by blocking sympathetic impulses that initiate detumescence while also causing paralysis of the retractor penis muscle. Priapism in association with phenothiazine-derivative tranquilizers develops more often in stallions and may be a consequence of their high androgen concentrations.

Mechanisms for priapism in men have been more thoroughly investigated than in animals. To gain some insight to the mechanisms responsible for priapism in animals, a brief discussion of the disorder in men is appropriate. In men, priapism is classified as high flow (arterial) when an increase in arterial blood flow overrides the compensatory venous drainage, or low flow (ischemic or venoocclusive) when the neural mediation of vascular tone is altered or primary vascular or hematologic alterations occur.[6]

Unlike low-flow priapism, which is usually very painful, high-flow priapism is usually not painful, produces a rigid to semirigid engorgement of the entire penis, and almost always results from blunt or penetrating trauma to the perineum or penis.[6] Injury results in direct communication of the arteries and lacunar spaces, bypassing the high-resistance helicine arterioles.[6] High-flow priapism is rare compared with low-flow priapism.[6] If the etiology of the priapism is unclear or repeated injections of phenylephrine fail to achieve detumescence, color-flow Doppler may confirm high-flow priapism by demonstrating an arterial-cavernosal fistula with high systolic flow into the cavernosal artery.[7]

Blood gas analysis of a sample aspirated from the cavernosum may be useful for distinguishing low-flow priapism from high-flow priapism. Low-flow priapism is suggested by a pH less than 7.25, PO_x less than 30 mm Hg, and PCO_x greater than 60 mm Hg.[7] The prognosis for men with high-flow priapism is better than for men 616 with low-flow priapism, because in low-flow states stagnation of blood occurs leading to increased carbon 617 dioxide content of the blood, increase in blood viscosity, edema, and, eventually, fibrosis. Although application of the high-flow and low-flow classification system used in humans to domestic animals may be pathophysiologically sound, there are no reports of traumatically induced (high-flow) priapism in animals.

141.3.1.1 Box 141-2 Causes of Priapism

- Acepromazine
- Amphetamines
- Mating mishaps
- Penile thromboembolism

- Spinal cord lesions associated with:
    - Distemper encephalomyelitis
    - Trauma
    - Nematodiasis
- Cauda equina lesions
- Castration
- Constipation
- Neoplasia
- Purpura hemorrhagica
- Severe constitutional distress
- Lower urinary tract irritation secondary to septic or nonseptic inflammation

Proposed mechanisms for low-flow priapism in men include the failure of endothelin production necessary for smooth muscle contraction, inhibited α-adrenergic stimulation, altered vascular endothelial cell function leading to thrombosis, altered intracellular metabolism of cofactors because of the hypoxic and acidotic environment, and phosphodiesterase 5A dysregulation of nitric oxide production.[7] Although nitric oxide is a major contributor to the normal erectile process, an investigation demonstrated that nitric oxide does not play a role in cavernous relaxation in the ischemic, acidotic environment associated with priapism. In cases of malignancy-induced priapism, sluggish blood flow can result from increased viscosity due to severe leukocytosis or, alternatively, outflow of blood from the penis may be obstructed by local tumor cell infiltration.[7]

Priapism in human beings, horses, and cats results from a selective engorgement of the corpus cavernosum. In men, the corpus spongiosum is less turgid during priapism than during normal erection. Reports in cats describe histologic findings supportive of selective engorgement of the corpus cavernosum.[8] In the dog, some reports define priapism as a selective engorgement of the corpus cavernosum, but case descriptions lend little support.[9] One report of a dog with priapism implied engorgement of the corpus spongiosum by the treatment of the priapism, but the corpus cavernosum of a cat described in the same report was the portion of the penis involved.[9] Another report of a dog with priapism does not indicate what portion of the penis was engorged, but it described how the disorder was diagnosed with a cavernosogram by injection of an iodinated contrast agent into the bulbus glandis. The bulbus glandis is actually a portion of the corpus spongiosum in the dog, and the contrast procedure should have been termed a *spongiosogram,* lending support to the premise that priapism in the dog involves the corpus spongiosum, not the corpus cavernosum as in other species.[9]

In humans characteristic histologic changes have been described in patients with low-flow priapism. Early degeneration of the trabecular pattern was observed within 12 to 24 hours after onset of priapism. After 48 hours, thrombus formation within cavernous spaces and necrosis of smooth muscle and nerves was extensive. Although late histologic changes have been described in a cat and in the horse, there is little knowledge of the early sequence of pathologic changes in domestic animals with priapism. Priapism induced with intracavernosal papaverine in a dog model resulted in early histologic changes typical of fibrosis, including sporadic endothelial defects, loss of plasma membrane integrity, and cytoplasmic condensation. However, this artificial model may not be typical of naturally acquired priapism in dogs, because it affects the corpus spongiosum instead of the corpus cavernosum. Gene expression of transforming growth factor (TGF)-l may be a mediator of fibrosis secondary to priapism.

141.3.2 Diagnosis of Priapism

A complete history should be obtained to identify potential causes, including drugs, breeding mishaps, neurologic disease, and trauma. A general physical examination should be performed to identify coexisting conditions that might serve as a cause for the priapism or contradict drug therapy. Physical examination of the penis reveals it to be erect but otherwise normal in the early stages. Likewise, the prepuce is anatomically normal. If the penis is examined after prolonged exposure to the environment, edema, tissue drying, and even necrosis may be observed. Although high-flow priapism has not been reported in the dog or cat, diagnostic tests used in men to separate high-flow from low-flow priapism may be useful if a history of trauma to the perineum or penis is identified. These tests include blood gas analysis of blood aspirated from the penis and color-flow Doppler studies to identify an arteriovenous fistula.[7]

141.3.3 Treatment of Priapism

Initial treatment of priapism should begin with identification and, if possible, elimination of the inciting cause. Although symptomatic therapy such as massage and topical agents maintains a moist environment and is appropriate, the priapism may not resolve. High-flow priapism is treated initially by observation, compression dressings, and cold packing. If the condition persists or the viability of the penile tissue deteriorates, selective pelvic arteriography with embolization or open arterial ligation is indicated.[7]

Numerous medical therapies, including diuretics and glucocorticoids, have been suggested for low-flow priapism; most have produced inconsistent or inadequate results.[8] Low-flow priapism secondary to infiltrative disease or blood dyscrasias is managed with symptomatic therapy and by addressing the primary disorder. When it results from idiopathic, neurologic, or pharmacologic causes, it is often managed by corporal aspiration, saline lavage, and intracorporal injection of phenylephrine.[7]

β-Agonists have been used to improve penile venous dilation. Drainage has also been suggested, but caution should be exercised when using β-agonists if cardiovascular disease is present.[8] When priapism is the result of α-adrenergic blockade (e.g., acepromazine administration), benztropine mesylate (an anticholinergic agent) may be of benefit. Other drugs such as diphenhydramine and terbutaline, which also have anticholinergic action, may be of benefit in animals. Several investigators have reported a wide range of responses with terbutaline but, overall, it appears to be of limited benefit. Use of α-adrenergic and β-adrenergic agonists for the management of priapism in animals still needs to be investigated.

Excessive oxygen free radicals, produced when ischemic tissue is reperfused, cause extensive tissue damage. Oxygen free radical scavengers, such as allopurinol, limit the extent of lipid peroxidation–induced tissue damage in experimental models.[7] The role of oxygen free radical scavengers in clinical priapism is unknown but warrants further investigation. Limited research demonstrates early onset of histologic changes associated with fibrosis. The changes are associated with gene expression of TGF-1 messenger ribonucleic acid. Therefore management may also involve anti-TGF beta agents to lessen or prevent fibrotic changes from occurring in the penis during priapism.

Anecdotal drug therapies, including topical ethyl alcohol, oral β-blockers, intracavernosal streptokinase, and methylene blue administration, have been reported in humans.[7] Their efficacy and safety in animals are largely unknown and their use should generally be avoided until both can be established.

In humans, surgical intervention is usually advised if detumescence cannot be achieved by medical therapy within 12 to 36 hours. The corpora cavernosum-to-glans spongiosum shunt is the preferred technique in humans. Alternatively, the Winter procedure (multiple Tru-cut needle cores of the corpus cavernosum) can be done. In the horse, aspiration of inspissated blood or lavage of the corpus cavernosum with heparinized saline using 12-gauge needles inserted into the corona glandis and base of the scrotum may resolve the priapism and is the procedure of choice for initial treatment. Return of fresh blood through the egress needle suggests a positive prognosis. This is similar to simple aspiration, advocated in humans. Saphenous vein–to–corpus cavernosum shunts, and corpora spongiosum–to–corpus cavernosa shunts are recommended only in humans as a last resort because of high impotence rates. In horses, a corpus cavernosum–to–corpus spongiosum shunt can be created to allow egress of blood from the corpus cavernosum and achieve detumescence.

Impotence rates in men treated with spongiosum-to-cavernosum shunts range from 40% to 75%. Whether such high impotence rates would also occur in dogs and cats is unknown but should be considered, and the owner apprised of the risk if a shunting procedure is attempted. The issue of impotence in stallions is less clear, because shunts created in normal horses failed to interfere with erection and ejaculation. Impotence in horses with priapism may be due to the damage created by the priapism episode and not the shunt itself. Pharmacologic management of impotence in domestic animals after priapism may be possible with vasoactive drugs such as phenoxybenzamine, papaverine, and phentolamine, but the effects are unknown.

Application of these surgical procedures in dogs and cats has not been investigated. Late histologic changes and intraoperative findings described in cats[8] support the pathogenesis of selective venous outflow obstruction of the corpus cavernosum. It therefore seems reasonable that such procedures might be successful in cats. However, the extremely small size of the involved structures would make execution of the procedures difficult.

Because the pathophysiology of priapism in dogs has been poorly described, it is impossible to know if such shunting procedures would be successful. The only case report describing the portion of the canine penis involved in a case of priapism[9] described incision of the bulbus glandis and pars longa glandis, both parts of the corpus spongiosum. If the corpus spongiosum is preferentially engorged or both corpora are affected in cases of canine priapism, then the shunting procedures described for treatment of men and horses may be of little benefit in dogs. Better definition is needed of the specific structures and pathophysiology involved in canine priapism.

Although shunting procedures remain untried in dogs, simple incision of the tunica albuginea of the corpus spongiosum followed by manual expression of hypoxic, viscous blood and lavage with heparinized saline in a dog and cat resulted in detumescence and salvage of the penis.[9] Whether aspiration and irrigation, shunting, or simple incision is attempted, priapism failing to respond to medical therapy should be managed surgically to prevent impotence or penile necrosis. If partial necrosis of the penis is present, partial penile amputation can be performed with some chance of preventing impotence. If extensive penile necrosis occurs, amputation and urethrostomy must be performed to save the animal. Impotence or penile amputation will have devastating economic consequences for breeding animals.

141.4 CONCLUSION

Priapism is an uncommon but potentially serious condition. The pathophysiology of priapism in domestic animals appears somewhat analogous to that of humans, but anatomic structures involved in dogs are not well described, and further work in this area is needed. Given the potentially devastating consequences of treated priapism, it would seem prudent on the part of the veterinarian to maintain an appropriate level of awareness to allow early identification and treatment of the condition. Treatment should begin with correction of underlying causes, when possible, and less invasive maneuvers such as saline lavage and instillation of phenylephrine. Surgical therapy for priapism should be pursued only when symptomatic and pharmacologic methods fail to achieve detumescence.

141.5 SUGGESTED FURTHER READING*

SA Gunn-Moore, PJ Brown, PE Holt, et al.: Priapism in seven cats. *J Small Anim Pract*. **36**, 1995, 262, *One of the few multicase studies of priapism in cats and the only report that reviews the histologic changes that occur with priapism.*

N Muruve, DH Hosking: Intracorporeal phenylephrine in the treatment of priapism. *J Urol*. **155**, 1996, 141, *Article that addresses the newer concept of pharmacologic treatment of priapism.*

SE Pautler, GB Brock: Priapism from priapus to the present time. *Urol Clin North Am*. **28**, 2001, 391, *A current and thorough review of all aspects of priapism and its management in humans.*

MC Rochat: Priapism: A review. *Theriogenology*. **56**, 2001, 713, *The most comprehensive and current review of priapism in the veterinary literature.*

ME Somerville, SM Anderson: Phallopexy for treatment of paraphimosis in the dog. *J Am Anim Hosp Assoc*. **37**, 2001, 397, *An article that reviews the phallopexy technique in a very readable format.*

* See the CD-ROM for a complete list of references.

142 Chapter 142 Mastitis

Kristi L. Dosher, DVM

142.1 KEY POINTS

- Mastitis primarily affects the postpartum bitch; occasionally it affects the queen and the pseudopregnant bitch.
- Mastitis may affect only one section of a mammary gland, multiple sections of a mammary gland, or multiple mammary glands.
- Chronic cases may be asymptomatic.
- Severe cases may be life threatening.
- The bacteria most commonly cultured include *Escherichia coli,* staphylococci, and β-hemolytic streptococci.
- Determination as to whether the neonates should continue to nurse should be based on antibiotic choice, neonate age, and if there is abscess formation or gangrene.
- Antibiotic selection may be determined using culture and sensitivity and pH of the milk, as well as whether or not the neonates will continue to nurse.
- Abscessed or gangrenous mammary glands require surgical drainage and debridement.
- Prognosis is good for most cases with appropriate treatment.
- Inflammatory adenocarcinoma may mimic mastitis.

142.2 INTRODUCTION

Mastitis is a condition that primarily affects the postpartum bitch. Occasionally pseudopregnant, lactating bitches will be affected. The anatomy of the teat includes a teat orifice, teat canal, teat sinus, and gland sinus (Figure 142-1).[1] Additionally each gland sinus is separated by connective tissue. Therefore mastitis can be diffuse, among multiple glands, or localized within one gland. The clinical picture can vary widely from life-threatening sepsis to no apparent clinical signs.

142.3 ETIOLOGY

The etiology is largely unknown. Risk factors include hematogenous spread, poor hygiene, environmental conditions, and trauma from the neonates. Although there are no published data on breed predisposition, it appears that breeds with short legs and pendulous mammary glands are at greater risk of trauma. The bacteria most typically cultured are *Escherichia coli,* staphylococci, and β-hemolytic streptococci.[2-4]

142.4 CLINICAL PRESENTATION

The clinical picture can vary from critically ill to asymptomatic with a history of the neonates failing to thrive. The affected gland or glands may be hot, swollen, firm, and painful. Severely affected cases can manifest fever, depression, lethargy, and anorexia. Some animals may arrive in septic shock. Abscess formation or gangrene is sometimes noted in severe cases of mastitis.

142.5 DIAGNOSIS

Normal canine milk can vary from yellow (colostral milk) to white, depending on the length of time post whelping. Milk from bitches with mastitis may appear normal, purulent, or reddish brown. The cytology of normal milk is very cellular, containing large numbers of neutrophils and macrophages.[2] Therefore it is important to interpret cytology with care. Smears from bitches with mastitis will be cellular but will have many free and engulfed bacteria.

Systemically ill patients may have alterations in the complete blood count and chemistry panel. It is not uncommon to see leukocytosis with a left shift or, in septic patients, leukopenia. Dehydration may cause elevations in packed cell volume, total protein, and blood urea nitrogen.

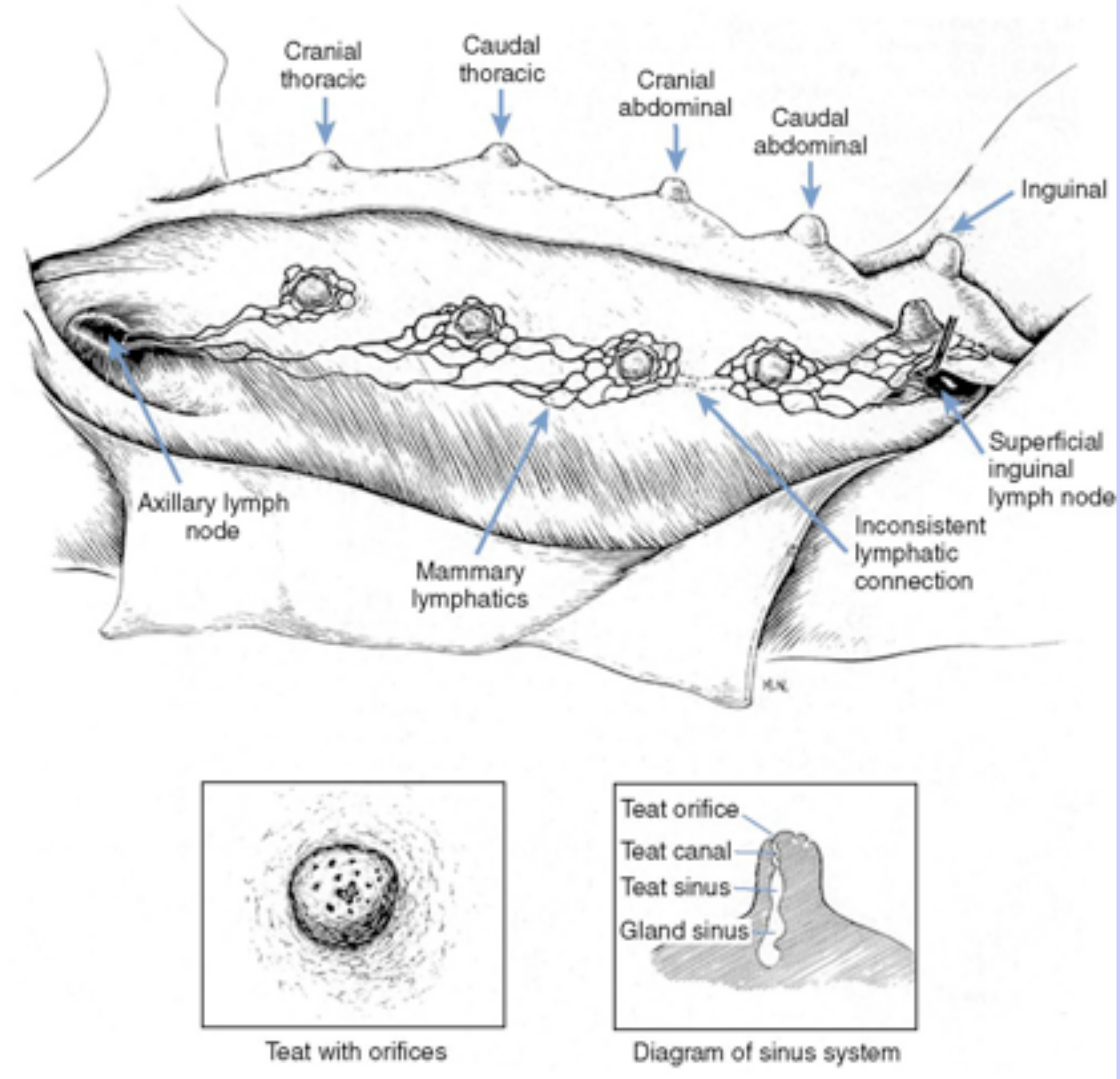
142.6 TREATMENT

142.6.1 Acute Mastitis

Treatment of bitches with mastitis should be based on antimicrobial sensitivity, pharmacokinetics of the antibiotic choices, and whether or not the neonates will be allowed to continue to nurse. Nursing should not be allowed if abscess formation or gangrene is present. Otherwise, nursing is an excellent way to drain the gland or glands. Bitches without nursing neonates will need to have the glands milked several times per day. If continued nursing is a viable option, antibiotic choice should be based on the safety of the neonate. While waiting for the sensitivity results, good antibiotic choices for nursing neonates would be first-generation cephalosporins and β-lactamase–resistant penicillins.[2] If a gram-negative infection is suspected, cefoxitin or chloramphenicol may be necessary[2] (see Chapters 108 and 109, Gram-Positive Infections and Gram-Negative Infections, respectively). Tetracyclines and quinolones are contraindicated in patients that will continue to nurse. In addition to antimicrobial therapy, it is important to apply hot packs to the affected area several times per day.

Systemically ill patients will require more intensive treatment. They may be in septic shock and require hospitalization for fluid therapy and intravenous antibiotics (see Chapters 106 and 107, Sepsis and Septic Shock, respectively). It is quite possible that these patients will not be able to care for their young, so the client should be informed of the time-intensive commitment of hand-feeding neonates. The typical time for mastitis to occur is during the first 2 weeks postpartum.[2] In these cases the offspring will need to be fed every 2 to 4 hours. If mastitis occurs later than 3 weeks postpartum, it will be possible to spread out the feedings to every 4 to 6 hours and begin weaning to a more solid diet.

Figure 142-1 Anatomy of the canine mammary glands. From Evans HE, Christensen GC: The urogenital system. In Evans HE, editor: *Miller's anatomy of the dog,* ed 3, Philadelphia, 1993, Saunders, with permission.



142.6.2 Gangrenous Mastitis or Abscess Formation

Some cases of acute mastitis will progress to gangrenous mastitis or abscess formation. Gangrene will be apparent by the presence of black, dead tissue in the area of the affected gland. In these cases the offspring should be removed from the dam and hand reared. These cases require surgical intervention. The gland should be incised, drained, debrided, and flushed. In severe or unresponsive cases, the affected gland may need to be removed (Color Plate 142-1).

142.6.3 Chronic Mastitis

Patients with chronic mastitis may have only a history of offspring that fail to thrive. These cases should be approached diagnostically the same way as are cases with acute mastitis. However, these cases may need more careful consideration when choosing antibiotics. In acute cases there is much inflammation, and the milk-plasma barrier is crossed easily by most antibiotics. In chronic cases, the inflammation has subsided and the barrier is intact. Because of this barrier it is important to choose antibiotics based not only on the sensitivity results, but also on the pH and lipid solubility.[2,4] Normal milk is slightly more acidic than plasma, so an antibiotic that is a weak base and that is also lipid soluble would be the most appropriate choice (Table 142-1).

142.6.4 Inflammatory Mammary Adenocarcinoma and Galactostasis

It is very important to consider inflammatory mammary adenocarcinoma in atypical bitches that are being evaluated for mastitis. This is a highly malignant neoplasm that typically affects older bitches. These patients may have the same clinical signs as a bitch with acute mastitis, but they are usually not postpartum. The mammary gland or glands are severely inflamed and these patients can be very ill. Disseminated intravascular coagulopathy and thrombocytopenia are not uncommon findings.[2,4]

Galactostasis is defined as the delay in the passage of milk from the mammary glands. Galactostasis can occur with mastitis but may also occur in the absence of disease. An example would be sudden weaning. The mammary glands will become hot, firm, and painful, but the patient is not systemically ill. It is important to determine the etiology quickly. A patient with galactostasis without mastitis will have cytology findings that can be cellular in nature, but intracellular bacteria are not noted. Treatment for these patients includes decreasing caloric intake for a few days, cool compresses, and steroids to reduce inflammation if infection is not present.

142.7 PROGNOSIS

The prognosis for mastitis is typically good. These patients do well with appropriate care and are not likely to have repeat episodes with additional litters. Most patients will be able to nurse their litters successfully unless they have had severe scarring. The prognosis for patients that present in septic shock should be based on the individual case and have a more guarded prognosis during the initial period.

Table 142-1 Lipid Solubility and Acid-Base Properties of Antibiotics

Drug	Lipid Solubility	Acid-Base
Ampicillin	Moderate	Acid
Amoxicillin	Moderate	Acid
Cephalothin	Low	Acid
Chloramphenicol	High	Alcohol
Ciprofloxacin	High	Amphoteric
Clindamycin	High	Base
Enrofloxacin	High	Amphoteric
Erythromycin	High	Base
Gentamicin	Low	Base
Penicillin G	Moderate	Acid
Sulfamethoxazole	Moderate	Acid
Sulfadiazine	Moderate to high	Acid
Tetracycline	Moderate	Amphoteric

Data from Johnston SD, Kustritz MVR, Olson PNS: *Periparturient disorders in the bitch: canine and feline theriogenology,* ed 1, Philadelphia, 2001, Saunders; and Olson JD, Olson PN: Disorders of the canine mammary gland. In Morrow DA, editor: *Current therapy in theriogenology: diagnosis, treatment, and prevention of reproductive diseases in small and large animals,* ed 2, Philadelphia, 1986, Saunders.

142.8 SUGGESTED FURTHER READING*

HE Evans, GC Christensen: The urogenital system (the mammae). In HE Evans (Ed.): *Miller's anatomy of the dog*. ed 3, 1993, Saunders, Philadelphia, *In-depth information and figures pertaining to anatomy*.

EC Feldman, RW Nelson: In *Canine and feline endocrinology and reproduction*. ed 3, 2004, Saunders, St Louis, *A comprehensive text with much useful information*.

SD Johnston, MVR Kustritz, PNS Olson: In *Periparturient disorders in the bitch: canine and feline theriogenology*. ed 1, 2001, Saunders, Philadelphia, *One of the most in-depth and comprehensive texts regarding mastitis in the bitch and queen*.

JD Olson, PN Olson: Disorders of the canine mammary gland. In DA Morrow (Ed.): *Current therapy in theriogenology: diagnosis, treatment, and prevention of reproductive diseases in small and large animals*. ed 2, 1986, Saunders, Philadelphia, A comprehensive reference about mastitis.

* See the CD-ROM for a complete list of references

143 Chapter 143 Preoperative Evaluation of the Critically ill Patient

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143.1 KEY POINTS

- A systematic approach to any critically ill patient is necessary to improve anesthetic and surgical outcome.
- An animal's airway, breathing, and circulatory status should be examined and stabilized first, before other vital organ systems are evaluated.
- Evaluation of the coagulation status and possible requirement for blood product administration is essential in the preoperative evaluation of the critically ill patient.

143.2 INTRODUCTION

Careful assessment of the critically ill small animal patient can make the difference between surgical success or failure and, in particular, the difference between the animal's life and death. The primary objective of evaluation of the preoperative patient is to recognize and treat any conditions that will increase the risk of anesthetic and surgical complications.[1,2] In addition, preoperative evaluation may provide some indication of the likely outcome for the patient (see Chapter 3, Survival Prediction Index).

Evaluation of the animal's signalment, history, physical examination, diagnostic tests, and presumed anesthetic risk are essential. Triage and physical examination are of particular importance when evaluating the critically ill patient (see Chapters 1 and 2, Physical Examination and Patient Triage, respectively). The respiratory, cardiovascular and hematologic systems are of primary importance when considering anesthetic and surgical risks. The clinician should use a step-by-step approach to each patient, to ensure that all necessary information regarding these systems is obtained before anesthesia induction.

Part of the assessment of the preoperative patient is the choice of an appropriate anesthetic protocol (see Chapter 163, Anesthesia of the Critically Ill Patient).

143.3 RESPIRATORY RESUSCITATION

Any sign of respiratory distress and hypoxemia should be corrected with supplemental oxygen therapy. An arterial blood gas analysis may not be feasible and may cause untoward distress for the critically ill patient. Therefore noninvasive evaluation of respiratory status with pulse oximetry and visualization of the animal's respiratory effort can be used to determine response to oxygen therapy. Once the animal is able to tolerate the procedure, thoracic radiographs should be performed to determine whether pulmonary parenchymal (contusions, pneumonia, pneumonia, edema), pleural space (pneumothorax, diaphragmatic hernia), or thoracic cage (rib fractures) abnormalities are present. Thoracic radiographs are always recommended before a major surgical procedure to rule out abnormalities that may affect the patient's ability to tolerate anesthesia, as well as to look for evidence of neoplasia that may alter the prognosis and hence the owner's expectations for the animal (see the Respiratory Disorders section of this text).

143.4 CARDIOVASCULAR RESUSCITATION

Hypovolemic shock is the most common cause of cardiovascular compromise in the critically ill patient and needs to be resolved before anesthesia induction. Clinical signs of hypovolemic shock include prolonged capillary refill time, tachycardia or bradycardia, hypotension, pale mucous membranes, and decreased urine output. A more thorough explanation regarding clinical signs and treatment of various forms of shock are listed elsewhere in this text. If pulse deficits, bradycardia, tachycardia, or an irregular heart rhythm is noted on physical examination, an electrocardiogram is indicated and specific therapy administered as appropriate (see Chapters 45, 46 and 47, Bradyarrhythmias and Conduction Abnormalities, Supraventricular Tachycardia, and Ventricular Tachyarrhythmias, respectively).

143.5 PAIN

Pain has numerous systemic consequences, slows recovery, and can prevent adequate assessment of the patient. Adequate analgesia is an essential aspect of stabilization of the critically ill patient. A variety of pain scoring systems have been used to document the severity of pain in animals.[3] In some cases pain assessment is easy, when the animal exhibits obvious signs of distress such as yelping, splinting or guarding of the injured site, or lameness. Some individuals, however, appear more stoic and, rather than display abnormal behaviors, demonstrate a lack of normal behaviors as their only sign of discomfort (see Chapter 161, Pain and Sedation Assessment and Analgesia). Analgesic drugs should never be withheld, even in the most critically ill patient. Opioid drugs do not adversely affect the cardiovascular system and are safe to use in even the most critically ill animals. Administration of a preanesthetic drug not only acts as an analgesic, but also decreases the total dosage of drug(s) required for anesthesia induction and maintenance (see Chapters 162, 163 and 164, Sedation of the Critically Ill Patient, Anesthesia of the Critically Ill Patient, and Constant Rate Infusions, respectively).

143.6 GLOBAL ASSESSMENT

Following adequate stabilization of the respiratory and cardiovascular systems and effective analgesia, a more detailed evaluation of the patient can be performed. The patient's neurologic status should be evaluated. Seizure activity requires immediate anticonvulsant therapy and, when present, is of higher priority than the ABCs (airway, breathing, circulation). Seizures can be associated with a metabolic disorder such as hypoglycemia, or they can be associated with an increase in intracranial pressure, cerebral edema, or a primary brain disorder. If a spinal injury is suspected, the patient should be immobilized immediately. The neck and pelvis are immobilized with tape, with the patient secured on a flat hard surface, to prevent further spinal cord destabilization, which can cause further injury. Neurologic abnormalities in the preoperative patient may influence the anesthetic and/or surgical management, in addition to the prognosis, and should be discussed with the owner. For example, if increased intracranial pressure is of concern, inhalant anesthetics should be avoided and mechanical ventilation is indicated to tightly control the partial pressure of carbon dioxide (PCO_2).

Obvious orthopedic fractures or luxations should be stabilized after provision of adequate analgesia and sedation.Penetrating injuries or open fractures should be treated as soon as possible, although this must wait until the cardiovascular and respiratory systems have been stabilized. In the meantime, administration of a first-generation cephalosporin should provide sufficient antimicrobial coverage to prevent infection until definitive surgical repair can be performed.

Global assessment of internal organs can be obtained by evaluating serum biochemical analyses and a complete blood count, if available. Abdominal ultrasound will further aid in identifying organ abnormalities, may be readily available on an emergency basis, and may help determine the nature of surgery required, the risks, and the associated prognosis.

143.7 LABORATORY TESTING

Part of the assessment of the critically ill patient is evaluation of key laboratory parameters. This is particularly important in the preoperative patient before anesthesia induction. Recommended minimal laboratory evaluation before surgery includes a packed cell volume, total solids, blood glucose, lactate, electrolyte, and acid-base evaluation. A full serum biochemistry panel and a complete blood count are ideal but may not be feasible in an emergency situation. In the absence of this information, evaluation of a blood smear for an estimated platelet and neutrophil counts may be beneficial.

Serum electrolyte and acid-base abnormalities should be corrected before anesthesia induction. Hyperkalemia, hypocalcemia, and hypoglycemia are of particular concern and require immediate intervention (see Chapters 55, 56 and 69, Potassium Disorders, Calcium Disorders, and Hypoglycemia, respectively). Serum lactate can be used as an indicator of global organ perfusion. An elevation in serum lactate concentration is often observed in cases of organ ischemia, hypovolemic shock, and septic shock. Reports have demonstrated a positive correlation between hyperlactatemia and mortality,[4] and serial measurements of serum lactate following administration of intravenous fluids can be used to determine how an animal is responding to treatment. Correction of hyperlactatemia is ideal. Worsening hyperlactatemia after volume correction is a poor prognostic indicator in the critically ill patient.

143.8 COAGULATION

Coagulation status should be determined before surgery. Activated partial thromboplastin time, prothrombin time, and buccal mucosal bleeding time should be obtained. An activated clotting time can be measured if activated partial thromboplastin and prothrombin times are not readily obtainable. A baseline platelet count should also be performed. If severe thrombocytopenia is present (platelet counts less than 20,000 to 30,000 cells/μl) preoperatively, administration of platelet-containing blood products may be indicated. If hypocoagulability is present, replenishment of clotting factors with fresh frozen plasma and vitamin K should be considered. In cases of suspected von Willebrand disease, fresh frozen plasma, whole blood, or cryoprecipitate can replenish von Willebrand factor. Administration of desmopressin (DDAVP) to the donor before collection of plasma or whole blood can increase the amount of von Willebrand factor available for the recipient (see Chapters 118 and 119, Bleeding Disorders and Thrombocytopenia, respectively).

143.9 BLOOD TYPE AND CROSSMATCH

Even during the most routine surgeries, blood loss is possible. Critically ill patients may be at greater risk of blood loss, and they are likely to be less tolerant of hemorrhage. Ideally, animals should be given only appropriately cross-matched red blood cell products, but this may not be feasible in the emergency setting. When cross-matching cannot be performed, assessment of blood type compatibility between the recipient and donor is recommended. In life-threatening hemorrhagic shock it may be necessary to administer unmatched, untyped blood products. Oxygen carrying capacity is ideal with a packed cell volume (PCV) of 30% or more. If an animal has clinically apparent anemia, with signs of lethargy, inappetence, tachycardia, or tachypnea, administration of whole blood or packed red blood cells should be considered before induction of anesthesia and surgery. In the emergency patient, hemoglobin-based oxygen carriers can also be administered until type-specific blood products are available. In general, the “Rule of Ones” states that administration of 1 ml of whole blood per 1 lb (2.2 ml blood/kg) will raise the recipient's PCV by 1%.[5] If the calculated dosage is insufficient to cause the predicted rise in the animal's PCV, blood loss is usually ongoing (see Chapter 66, Transfusion Medicine).

143.10 CONCLUSION

In conclusion, preoperative evaluation of the critically ill patient must be approached in a careful, step-by-step manner. The respiratory and cardiovascular systems are of particular importance, and all efforts should be made to stabilize animals before anesthesia induction. If a patient is not readily stabilized, the clinician must decide if the urgency and benefits of surgery outweigh the risks of the procedure. In some situations delaying surgery until the patient's status has improved may be desirable.[1]

143.11 SUGGESTED FURTHER READING*

TW Fossum: Preoperative assessment of the surgical patient. In TW Fossum (Ed.): *Small animal surgery*. ed 2, 2002, Mosby, St Louis, *A good reference tool to use in the approach to the small animal patient before induction of general anesthesia and surgery*.

E de Papp, KJ Drobatz, D Hughes: Plasma lactate concentration as a predictor of gastric necrosis and survival among dogs with gastric dilatation-volvulus: 102 cases (1995-1998). *J Am Vet Med Assoc*. **215**, 1999, 49, *Article describing the use of plasma lactate to predict gastric necrosis and risk of gastric resection and mortality in dogs with naturally occurring gastric dilation-volvulus*.

RE Syring, KJ Drobatz: Preoperative evaluation and management of the emergency surgical small animal patient. *Vet Clin North Am Small Anim Pract*. **30**, 2000, 473, *An excellent reference that provides a generalized approach to the critically ill small animal patient during the preoperative period.*

JC Thurmon, WJ Tranquilly, GJ Benson, et al.: Considerations for general anesthesia. In WV Lumb, EW Jones (Eds.): *Veterinary anesthesia*. 1991, Williams & Wilkins, Baltimore, *A chapter that describes a general approach to anesthesia and displays the scoring system to rank the severity of clinical disease in a small animal patient before induction of general anesthesia*.

AE Wagner, CI Dunlap: Anesthetic and medical management of acute hemorrhage during surgery. *J Am Vet Med Assoc*. **203**, 1993, 40, *Article describing management of anesthesia and acute hemorrhage, and formulas to calculate the amount of blood transfusion required to increase an animal's hematocrit.*

* See the CD-ROM for a complete list of references.

144 Chapter 144 Postoperative Evaluation of the Critically ill Patient

Elisa Mazzaferro, MS, DVM, PhD, DACVECC

144.1 KEY POINTS

- Particular concerns in the postoperative patient are abnormalities of the respiratory, cardiovascular, thermoregulatory, and hematologic systems.
- Hypoventilation, hypoxemia, hypotension, and hypothermia are some of the most common life-threatening abnormalities seen in the postoperative patient.
- Active rewarming is essential in the postoperative patient. Once the animal's core body temperature has been increased to 99° F, active rewarming efforts should stop, to prevent accidental hyperthermia.

144.2 INTRODUCTION

Getting a critical patient through surgery is just one of many hurdles that the clinician and animal will face before discharge from the hospital. During the immediate postsurgical period, careful patient assessment, monitoring, and nursing care can make the difference between life and death. Postoperative patients commonly have multisystem abnormalities as a result of their primary disease processes, surgical insult, and effects of anesthetic agents. Of particular concern are abnormalities of the respiratory, cardiovascular, thermoregulatory, and hematologic systems.

144.3 ANESTHETIC RECOVERY

144.3.1 Airway and Breathing

Careful monitoring of the patient's airway, breathing, oxygenation, and ventilation should continue throughout the postoperative period. If possible, a Wright's respirometer can be used to assess the animal's tidal volume (normal 10 to 15 ml/kg). During prolonged anesthesia and recumbency, dependent lung lobes can be atelectatic, causing intrapulmonary shunting of blood. The airway should remain intubated with a cuffed endotracheal tube until the patient can actively swallow and is actively fighting the endotracheal tube. If significant respiratory compromise is evident, it may be prudent to keep the patient intubated and initiate mechanical ventilation rather than place the patient at risk by extubation.

Vomiting or regurgitation of gastric contents is common during the immediate postoperative period. If this occurs, the pharyngeal region and esophagus should be suctioned and the esophagus flushed with sterile saline to prevent aspiration pneumonia and esophagitis. Routine use of antibiotics in animals with potential aspiration pneumonia should be avoided until there is evidence of pneumonia, because empiric antibiotic use can promote development of resistant bacterial organisms in the animal and hospital environment.

144.3.2 Hypoventilation

Anesthetic gases and pain can predispose a patient to hypoventilation. Hypoventilation is identified by elevated partial pressure of carbon dioxide levels on blood gas evaluation. While still intubated, the animal can be assessed noninvasively for hypoventilation with end-tidal carbon dioxide monitoring.[1] Hypoventilation most commonly results from increased dead space or inadequate minute ventilation. If hypoventilation is identified, the animal's respiratory rate and character should be monitored carefully. Apnea, bradypnea, or inadequate tidal volumes may require intermittent positive-pressure ventilation by hand or machine until the patient is able to ventilate effectively unassisted. Anesthetic agents and opioid analgesics can be potent respiratory depressants and can cause hypoventilation during the early postanesthetic recovery period. Excessive apparatus dead space will also cause hypercapnia and is to be avoided. Patients with persistent severe hypercapnia (partial pressure of arterial carbon dioxide >60 mm Hg) despite therapy are candidates for mechanical ventilation.

144.3.3 Hypoxemia

Oxygenating ability must be monitored closely during the postoperative period. If an animal has an arterial catheter, an arterial blood gas analysis with and without supplemental oxygen should be performed to determine arterial oxygenation.[2] If an arterial catheter is not available, noninvasive measures of oxygenation such as pulse oximetry should be used until the patient's oxygen saturation exceeds 95%. If oxygenation is inadequate, supplemental oxygen should be administered by oxygen cage or hood or nasal, nasopharyngeal, or tracheal oxygen catheterization.

Hypoxemia, identified as a partial pressure of arterial oxygen less than 80 mm Hg or an oxygen saturation of less than 95%, is most commonly a result of pulmonary parenchymal disease such as pulmonary edema, pulmonary contusions, pneumonia, atelectasis, or parenchymal dysfunction secondary to pleural space disease. In the patient breathing room air, hypoventilation can cause hypoxemia that will resolve rapidly with oxygen administration. If hypoxemia is identified, it should prompt the clinician to evaluate the patient thoroughly and perform further diagnostic tests as indicated.

144.4 CIRCULATORY STATUS

144.4.1 Hypotension

Critical illness and anesthesia are both common causes of hypotension, making intensive blood pressure monitoring essential during the postoperative period. Continuous direct arterial blood pressure monitoring is ideal in the critically ill patient; when it is unavailable, indirect measurement is done with an oscillometric and/or Doppler technique. Hypotension may be caused by hypovolemia, vasodilation, or decreased myocardial contractility. Initial therapy generally is focused on aggressive support of intravascular volume. Measurement of central venous pressure can help guide this therapy. If primary myocardial disease is suspected, echocardiographic evaluation is indicated and positive inotropic drugs such as dobutamine may be required.

Vasodilation is a potent cause of hypotension that is unresponsive to fluid administration. It is most commonly a result of anesthetic drug effects and/or a severe systemic inflammatory response during the postoperative period. Vasopressor drugs such as dopamine, norepinephrine, and vasopressin are usually required to support blood pressure in these patients.

Bradyarrhythmias and tachyarrhythmias can also cause hypotension and should be treated appropriately. Electrocardiographic monitoring can be very useful in the postoperative patient for early detection of dysrhythmias, as well as identification of tachycardia that can be an early warning sign of cardiovascular compromise, pain, or anxiety.

144.4.2 Oxygen Delivery

Oxygen delivery is dependent on arterial oxygenation, hemoglobin concentration, and the ability of the heart and circulatory system to deliver vital oxygen to end organs, including peripheral tissues. Factors that influence oxygen delivery include bradyarrhythmias or tachyarrhythmias, inadequate circulating intravascular fluid volume, inadequate hemoglobin concentration or oxygen carrying capacity, inadequate hemoglobin saturation of oxygen, and peripheral vasoconstriction that increases vascular afterload, hypothermia, and depressed myocardial contractility. Until anesthetic drugs have worn off or have been metabolized, inappropriate vasodilation with peripheral vasoconstriction, hypoventilation, and decreased myocardial contractility may also be present. Careful monitoring of cardiac rhythm, blood pressure, hemoglobin concentration, oxygen saturation, and core body temperature should be performed until all have normalized.

144.5 PAIN VERSUS DYSPHORIA

During the immediate postoperative period, it is often difficult to accurately differentiate between pain and dysphoria.[3] Recognition of pain in animals can be challenging because of interpatient and interspecies variations in manifestations of clinical signs of pain. Postoperative analgesia should be administered with the intent that the animal should never be allowed to be in pain.

Multimodal analgesia with opioids, nonsteroidal antiinflammatory drugs, and intrapleural or local administration of anesthetic agents can be performed to minimize patient discomfort and maximize analgesia without causing adverse side effects. It is still difficult to accurately assess whether an animal is in pain, attention seeking, or dysphoric. Physical examination parameters such as heart rate and blood pressure can be increased with pain, or they can be increased because of anxiety, dysphoria, or an animal's need to urinate or defecate in an area away from its immediate environment.

First, evaluate the surgical site for evidence of pain on palpation. If present, administration of additional analgesia may be necessary. If the animal's physical status is unchanged after additional anesthetic or analgesia, or if it does not respond to a painful stimulus at the surgical site, consider whether the animal's vocalization or thrashing improves with soothing voice and attention from the caregiver. If this improves the animal's outward manifestation of apparent pain, consider that the animal may be seeking attention. Finally, place a urinary catheter or allow the animal to urinate or defecate in an area away from its immediate environment, when possible, to eliminate this potential cause of stress. If all else fails, administration of an anxiolytic or partial reversal of an opioid with an agonist-antagonist or antagonist may be useful in diagnosing and treating apparent clinical signs of dysphoria.

144.6 HYPOTHERMIA

Hypothermia is a postoperative complication that can interfere with tissue offloading of oxygen from hemoglobin, cardiac performance, elimination of anesthetic wastes, coagulation, and wound healing.[4,5] Hypothermia can be prevented or minimized intraoperatively by using circulating warm water blankets, circulating warmed forced-air blankets, intravenous fluid warmers, and lavage of body cavities with warmed sterile fluids.[6] During the immediate postoperative period, anesthetic drugs will interfere with the body's normal physiologic mechanisms that create shivering.

The accessories mentioned above can also be used postoperatively to increase the animal's body temperature. Electric blankets and electric heating pads should never be used because of the risk of causing severe thermal burns.[7] Once the animal's core body temperature has been increased to 99° F, active rewarming efforts should stop, to prevent accidental hyperthermia.[6]

144.7 COAGULATION

Intravenous administration of large volumes of intravenous crystalloid or colloid fluids,[8] blood products,[9] and hypothermia can all lead to coagulation abnormalities. Anticoagulants used in blood products can bind with calcium and lead to poor muscular responsiveness. In animals with refractory perianesthetic hypothermia and hypotension that have received blood products, ionized calcium concentration should be measured, because hypocalcemia can interfere with arteriolar constriction and vascular tone. When present, hypocalcemia can be corrected with intravenous administration of calcium gluconate and careful infusion of calcium-containing crystalloids, such as lactated Ringer's solution.

True coagulopathies that have been documented by prolonged prothrombin time, activated partial thromboplastin time, or activated clotting time can be reversed partially with administration of activated clotting factors in fresh frozen plasma. Significant thrombocytopenia can also cause a coagulopathy, and patients with platelet counts less than 10,000 cells/μl may require platelet administration. Although platelet concentrate and platelet-rich plasma exist, they usually must be ordered from a commercial blood bank, so unfortunately are often not available during the immediate postoperative period.

Serial measurements of the animal's hematocrit can be performed to document and treat ongoing blood loss and anemia. In animals whose serial coagulation profiles indicate worsening thrombocytopenia, elevations in fibrin degradation products or D-dimers, and rapid or prolonged activated partial thromboplastin time or prothrombin time, or both, disseminated intravascular coagulation should be suspected.

144.8 ACID-BASE AND ELECTROLYTE STATUS

Acid-base, electrolyte, and glucose abnormalities are common during the immediate postoperative period. The animal's acid-base and electrolyte status should be evaluated at least once every 12 to 24 hours and in critical patients may be indicated every 2 to 4 hours. Fluid therapy should be tailored accordingly.

Metabolic acidosis can be associated with decreased organ perfusion and usually can be corrected once intravascular circulating volume and hypothermia have been corrected. Serial lactate measurements can be performed as an indicator of global organ perfusion and oxygen utilization. Serial elevations in peripheral lactate can be a poor prognostic indicator and suggests a lack of response to fluid and oxygen therapy. Severe metabolic acidosis with a pH less than 7.1 warrants aggressive intervention. Supplemental bicarbonate therapy may be indicated if therapy of the primary disease process is ineffective. A base deficit can be determined, and the dosage of bicarbonate required can be calculated with the following formula:

$$\text{Bicarbonate deficit } (\text{mEq HCO}_3^-) = \text{BW}_{\text{kg}} \times 0.4 \times (24 - \text{HCO}_3^-)$$

where BW_{kg} is the patient's body weight in kilograms.

Generally, only one third to half of this calculated dose is administered. Alternatively, a more cautious approach to normalizing the patient's metabolic acidosis is to administer immediately one fourth of the calculated bicarbonate dose, then administer the rest over a period of 4 to 6 hours.

144.9 WOUND CARE AND BANDAGING

An animal's wounds and bandages can be a source of nosocomial infection.[10,11] Further, a large percentage of nosocomial infections are acquired from direct contact with the hands of hospital personnel. Bandages should be checked frequently for evidence of soilage or strike-through. Any bandage that becomes wet or soiled should be changed immediately. The surgical site or wound should be checked at least once or twice daily for evidence of erythema, tenderness, pain, or drainage. Whenever a bandage is changed or the wound site is evaluated, personnel should wash their hands carefully and wear gloves to protect the patient from a potential source of infection. Catheter sites should be evaluated at least once daily for evidence of pain, thrombosis, erythema, or discharge. When signs are present, the catheter should be removed and the catheter tip cultured for bacteria.

144.10 NUTRITION

Enterocytes will atrophy within 48 hours of lack of luminal nutrients. Nutritional support is one of the most important aspects of promoting healing. Inadequate enteral nutrition can delay wound healing and promote bacterial translocation from the gastrointestinal tract, and thus increase patient morbidity, length of hospital stay and, potentially, mortality. At the time of surgery, an esophagostomy, gastrostomy, or jejunostomy tube should be 628 placed if an animal has been inappetent, or is at risk for inappetence during the postoperative period.[12-16] A 629 patient's daily caloric requirements (resting energy expenditure, or RER) can be calculated by the formula[17] RER in kcal $= (30 \times BW_{kg}) + 70$

If enteral nutrition is impossible, parenteral nutrition can be provided through a central venous or intraosseous catheter.[18] Supplemental feeding can be discontinued once the animal is able and willing to voluntarily consume its daily caloric requirements.

144.11 PATIENT CLEANLINESS

Patient cleanliness is of paramount importance during the postoperative period. Contamination of surgical sites with wound exudates, feces, urine, vomitus, or contaminants from the external environment can delay wound healing and promote infection. Wounds and surgical sites should be covered to prevent contamination from the outside. Moisture or strike-through of blood or wound exudates can promote wicking of bacteria from the environment into the wound. Any bandage with strike-through should be immediately changed and discarded. Immobile animals should have a urinary catheter in place to prevent urination into bedding and urine scald. Bedding should be well padded, soft, clean, and dry to prevent urine scalding, pressure necrosis, and decubitus ulcers.

144.12 PATIENT IMMOBILIZATION AND PHYSICAL THERAPY

Immobile animals are at particular risk for atelectasis, pneumonia, and decubitus ulcers. Nonambulatory or immobile animals should be turned from side to side and placed in sternal recumbency at least every 4 to 6 hours to promote adequate ventilation and prevent atelectasis in the dependent lung. Padding around pressure points (elbows, shoulders, hips, and stifles) should be thick and adequate to prevent pressure necrosis. Deep tissue massage and passive range-of-motion exercises should be performed 3 to 4 times daily to prevent disuse atrophy and dependent edema. Whenever possible, visitation with the animal's family and movement to the outdoors should be promoted to maintain the animal's mental well-being. Visits from caretakers in off times, without providing any therapy other than company and tender loving care, should also be included as part of the critical patient's daily treatment orders.[19]

144.13 CONCLUSION

Careful monitoring and assessment of the critically ill patient is challenging during the immediate postoperative period. Although anesthetic recovery is critical, other criteria including nutrition, cleanliness, and physical therapy are necessary to maximize the animal's well-being and promote wound healing. Analgesia and sedation should be maximized without causing dysphoria and agitation. Wound and bandage care is optimal in preventing postoperative infection. Kirby's Rule of Twenty[19] is discussed in Chapter 201, Daily Assessment of the Critically Ill Patient. This checklist can provide even the most astute clinician with a source of potential complications in the postoperative critically ill patient.

144.14 SUGGESTED FURTHER READING*

SR Armstrong, BK Roberts, M Aronsohn: Perioperative hypothermia. *J Vet Emerg Crit Care*. **15**, 2005, 32, *Describes the pathophysiology, recognition, adverse consequences, and treatment of perioperative hypothermia*.

CA Brady, LG King: Postoperative management of the emergency surgery small animal patient. *Vet Clin North Am Small Anim Pract*. **30**, 2000, 681, *Describes an approach to the critically ill postsurgical small animal patient, with special emphasis on recognition of systemic inflammatory response syndrome*.

HB Seim, MD Willard: Postoperative care of the surgical patient. In TW Fossum (Ed.): *Small animal surgery*. ed 2, 2002, Mosby, St Louis, *Describes the postoperative care and considerations in the small animal patient, with particular emphasis on nutrition and placement of feeding tubes*.

* See the CD-ROM for a complete list of references

145 Chapter 145 Postcraniotomy Management

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145.1 KEY POINTS

- Imaging studies ideally are performed immediately following surgery, while the patient is still under anesthesia.
- After anesthetic recovery, animals usually are monitored in a critical care area for signs of neurologic deterioration or other complications such as pneumonia for at least 48 hours.
- Oral food and water are withheld until the animal regains swallowing function, which may take a number of days.
- Maintaining cerebral blood flow is essential during the recovery phase following intracranial surgery.
- Poor ventilation and increasing partial pressure of arterial carbon dioxide ($PaCO_2$), such as from obstruction or crimping of the endotracheal tube, can lead to disastrous increases in brain volume, terminal brain swelling, and subsequent herniation.

145.2 INTRODUCTION

Intracranial surgery is employed most commonly for removal of intracranial masses, biopsy of intracranial lesions, placement of ventricular shunts, decompression and debridement of intracranial tissues, and treatment of increased intracranial pressure (ICP). Surgery may include removal of sizable portions of the skull (craniotomy or craniectomy) or be limited to smaller burr holes for decompression and evacuation of hematoma or stereotactic biopsy. Other indications for intracranial surgery in humans include seizures, chronic pain, and movement disorders.[1]

A consensus on the most appropriate postoperative management of animals after intracranial surgery is lacking. Many postoperative procedures are taken from similar experiences in humans. They are based on information regarding pathophysiologic alterations in the intracranial space and their treatments, as well as individual clinicians' anecdotal experiences.

145.3 POSTOPERATIVE MANAGEMENT

Immediately following surgery, while the patient is still under anesthesia, is the ideal time to perform an anatomic imaging study such as magnetic resonance imaging. The degree of lesion resection is assessed, as well as any intracranial complications associated with the surgical procedure such as cerebral edema, parenchymal damage, or hemorrhage (hematoma). Immediate surgical decompression is indicated if there is an expanding hematoma or if brain compression is significant.

After recovery from anesthesia, animals usually are monitored in a critical care or intensive care area for signs of neurologic deterioration for at least 48 hours. Animals should be kept in a comfortable, well-padded, and quiet environment with minimal light stimulation. Cerebral edema may evolve for up to 48 hours after injury and persist for a week or more.[2] Physiologic monitoring during the hours to days following intracranial surgery should be performed on a frequent, if not continual, basis. This type of monitoring commonly includes assessment of heart rate and rhythm, respiratory rate and character, blood pressure, blood gases, oxygenation, urine production and, in some instances, ICP through objective means. The goal of such monitoring is to maintain adequate cerebral blood flow without compromising other organs.

Cerebral blood flow is maintained primarily through support of systemic blood pressure using fluid therapy and vasopressive drugs if needed, at the same time preventing increases in ICP. Blood gas measurements or capnometer use aids in controlling respiration to prevent increases in $PaCO_2$ and subsequent cerebral vasodilation. Capnometer measurements, however, are usually less accurate than direct blood gas measurements.

ICP is monitored objectively in some situations; however, this type of measurement is not performed routinely in animals. ICP monitoring has been described in dogs and cats.[3-11] An advantage with this measure is that trends toward increasing ICP can be recognized early and treated before life-threatening increases occur.[12] An objective measure of ICP and blood pressure also allows for calculation of cerebral perfusion pressure (CPP) as a reflection of cerebral blood flow.

Disadvantages to invasive ICP monitoring include added surgery time for implantation of the monitoring system, expense, and the potential for iatrogenic brain damage from the monitoring system. Until some of these disadvantages are overcome, ICP monitoring will probably not become routine for animals undergoing intracranial surgery.[4,10] Newer, noninvasive techniques for measurement of the cerebral blood flow such as transcranial Doppler ultrasonography may provide an indirect measure of ICP.[13] Similar procedures and information have been investigated in dogs and cats.[14,15]

Neurologic parameters monitored include pupil size and responsiveness to light, level of consciousness, behavior, and the ability to move and walk. Cranial nerve abnormalities may provide important clues to underlying intracranial injury or deterioration.

Animals that have recovered from anesthesia are placed in a neutral or head-elevated position. Head elevation to 30 degrees above cardiac level decreases ICP primarily by facilitating venous drainage.[16-18] In humans it has been shown that CPP and cerebral blood flow are maintained in the 30-degree head elevation position and ICP is concurrently decreased.[16] There continues, however, to be debate about the degree of benefit of head elevation in animals following intracranial surgery.

Oral food and water are withheld until the animal is fully alert. With the combination of intracranial depressant effects of surgical manipulation and anesthetic or anticonvulsant drug therapies, appropriate swallowing, which prevents aspiration of oral contents, may take a number of days to return, putting the patient at risk for aspiration of oral contents (see Nonneurologic Complications later in this chapter). Stools are monitored regularly for melena that might indicate gastrointestinal (GI) ulceration. If noted, an antiulcer medication (e.g., ranitidine) is administered concurrently because of the apparent increase in GI ulcers in patients with neurologic impairment.

145.3.1 Hydration

Maintaining cerebral blood flow is important during the recovery phase following intracranial surgery. Cerebral perfusion depends on systemic blood flow and ICP and is expressed via the formula:

$CPP = MABP - ICP$ where CPP = cerebral perfusion pressure, MABP = mean arterial blood pressure.[19,20] For CPP to remain constant, the effects of increased ICP on blood flow to the brain must be reciprocated by increases in systemic blood pressure. CPP is a determinant of cerebral blood flow but is not always equivalent. In many instances, however, CPP is a reasonable reflection of cerebral blood flow.

Following clinical assessment, fluid resuscitation or fluid maintenance usually is performed with appropriate crystalloids or colloids. They are administered intravenously to maintain appropriate blood pressure and organ perfusion, including appropriate cerebral perfusion. The effects of fluid therapy should be monitored carefully, because overhydration with isotonic fluids may perpetuate brain edema, and dehydration may predispose to intracranial blood sludging and ischemia. Monitoring of systemic blood pressure and central venous pressure may help to reestablish normovolemia. Implantation of a central venous catheter should be performed cautiously in an animal with increased ICP, because manipulation or occlusion of the jugular vein for catheter placement may elevate ICP. Quick, efficient, and atraumatic jugular catheterization is a must in this situation.

145.3.2 Ventilation

Cerebral vessels are directly responsive to $PaCO_2$ concentrations, with cerebral blood flow coupled to cerebral metabolic rate. The cerebral vessels have the ability to change diameter in response to $PaCO_2$ (chemical autoregulation) and blood pressure (pressure autoregulation) in order to maintain a relatively constant cerebral blood flow. Cerebral vessels change diameter through perivascular changes in pH, occurring as a direct result of $PaCO_2$ concentrations.

As $PaCO_2$ concentrations increase, cerebral vessels dilate to increase blood flow to the brain. Poor ventilation and increasing $PaCO_2$, such as from obstruction or crimping of the endotracheal tube, can lead to disastrous increases in brain volume, terminal brain swelling, and subsequent herniation.[21] If autoregulation is intact, hyperventilation to decrease $PaCO_2$ will cause cerebral vasoconstriction, decreased cerebral blood volume, and subsequently decreased ICP.

Unfortunately, cerebrovascular autoregulatory capability is negatively affected by a variety of intracranial pathologies including local acidosis, which is common in many hypoxic and ischemic brain areas.[21] Animals often are hyperventilated during intracranial surgical procedures to maintain $PaCO_2$ in the range between 28 and 32 mm Hg, to prevent cerebral hypoxia from poor ventilation. During the postoperative period, ventilatory support may be indicated. Endotracheal intubation and ventilator support can be performed under the influence of barbiturate anesthesia or neuromuscular blockade. Appropriate ventilator management is imperative.

When ventilatory support is not immediately necessary or is not feasible, it is still important to recognize that decreased ventilatory effort or capacity may result in increases in ICP. Preventing atelectasis by frequent (hourly) movement of the animal from a lateral recumbent position may also be necessary.

145.3.3 Oxygenation

Along with maintenance of cerebral perfusion, maintenance of cerebral oxygenation is an important aspect of treatment of acute intracranial injury. Nasal oxygen administration may be helpful in an animal that has sustained trauma.

145.3.4 Sedation

Sedation may be necessary in animals requiring ventilatory management or when the animal is disoriented, at risk for further injury from excessive or uncoordinated movements, or if demented and vocalizing excessively. Forced expiration in these situations may result in increases in ICP. An in-depth review of sedative and anesthetic agents and their effects on the nervous system is beyond the scope of this chapter and have been reviewed elsewhere.[22-24] The choice of these agents depends on many factors, including ease of administration, rapidity and ease of induction and recovery, effects on cerebral metabolism and blood flow, alterations in ICP, and familiarity of the anesthetist with the anesthetic agent. Effects of anesthetic agents on ICP have also been reviewed elsewhere.[22-33]

Barbiturates can be used in some instances to decrease cerebral metabolism, cerebral blood flow, and subsequently ICP.[26] Barbiturates may benefit brain blood flow by causing vasoconstriction in normal tissue and by shunting blood to underperfused or ischemic areas. Other suggested benefits include decreases in vasogenic edema, decreased oxygen metabolism, decreases in intracellular calcium, and free radical scavenging.[26] Arterial blood pressure should be monitored closely, however, because barbiturates can result in hypotension, which may then decrease cerebral blood flow and increase cerebral ischemia.

Most inhalant anesthetic agents increase ICP as a result of their vasodilatory effects on cerebral vessels and subsequent increase in cerebral blood flow. Halothane, for example, causes the largest degree of cerebral vasodilation. Increases in cerebral blood flow can increase ICP because of the associated increase in intracranial volume.[27] Isoflurane is the most commonly used maintenance anesthetic agent for intracranial surgery[28] and has been used safely in both clinical and experimental studies involving intracranial surgery in dogs and cats.[3-9] Benzodiazepines may help, especially for short-term seizure control. Propofol is being used increasingly for anesthesia in animals with intracranial abnormalities.[29-33]

145.3.5 Pain Management

Pain is controlled with narcotics for at least 72 hours after surgery. Morphine, fentanyl, or codeine is used for this purpose in our hospital. Although these drugs have been shown to increase ICP, they are still used often for pain control in humans following intracranial surgery.[34-38] The level of pain associated with intracranial surgery may be less than that with other surgeries,[39] but pain control is still mandatory. Obviously, there is a need to balance analgesia in relationship to ongoing intracranial physiologic derangements. Some animals are delirious after surgery and vocalize, which may be mistaken for a pain response. Excessive exposure to sound and light should be kept to a minimum to prevent further stimulation.

145.3.6 Anticonvulsants

Many animals requiring intracranial surgery have seizures. These animals are often receiving anticonvulsant medications before surgery, and the medication should be continued during the postoperative period. If animals are not receiving anticonvulsants, and if the risk of seizures after surgery is significant, then anticonvulsant therapy should be begun before surgery. Anticonvulsant medications are used prophylactically in humans following intracranial surgery when the seizure risk is high or if any seizure will have a detrimental effect.[39]

Routine use of prophylactic anticonvulsant administration, however, has been questioned in some situations in humans, primarily because of the low overall risk of seizures after surgery and the medication side effects.[40,41]

Ideally, medications should be begun preoperatively so that therapeutic levels are stabilized before surgery. If potassium bromide is to be used, a longer period between initiation of the drug and surgery may be needed. Intravenous loading with sodium bromide has been described if surgery needs to be performed in a more expeditious manner.[42] Because of alterations in cerebral blood flow and systemic blood levels, levels of anticonvulsants may fluctuate widely during and after surgery (see Common Postoperative Complications later in this chapter).

145.3.7 Wound Management

A stockinet or similar light bandage may be placed over the incision. Holes are cut in the stockinet to allow the ears to be unrestricted. Gauze sponges may be placed under the stockinet to collect any discharge from the wound. A mildly compressive bandage helps decrease the chance of subcutaneous emphysema if the frontal sinus has been opened. Rarely, if an animal is excessively violent in its movements, a helmet-type or similar protective device can be used to prevent additional injury. Animals with excessive or violent movements should be sedated with diazepam (either bolus or constant infusion) or, in some instances, even acepromazine.

Incisions are examined daily for signs of inflammation. Oral food and water are withheld until the animal is fully alert. Unless the animal behaves normally and can walk, we do not give anything orally for up to 5 days after surgery to decrease the incidence of aspiration pneumonia (see Common Postoperative Complications later in this chapter).

145.3.8 Antibiotics

The necessity for preoperative and intraoperative antibiotics has been debated in human neurosurgery; there is support for prophylactic antibiotic administration in clean neurosurgical procedures.[43,44] Antibiotics most often are given for prolonged (>1.5 hour) procedures, if contaminated body cavities are to be opened (i.e., the nasal cavity), or if contamination is more likely (excessive number of individuals involved in surgery). Prophylactic antibiotics are usually first-generation cephalosporins (cephalothin 22 mg/kg IV q1.5h) until the end of the procedure. There is no information regarding the utility of routine prophylactic antibiotic administration following intracranial surgery. Antibiotics are indicated, however, for the specific infections that have been documented and identified in these animals.

145.3.9 Physical Therapy

After the acute effects of brain injury are controlled, the goal is to allow time for brain healing and recovery of function to occur. Smaller animals are often better candidates for prolonged nursing care than are larger animals because of the ease of manipulation. Good nursing care includes preventing decubitus ulcers in the recumbent animal and monitoring for secondary infections, mainly of the pulmonary and urogenital systems. Recumbent animals should be placed on clean, soft bedding and turned frequently (ideally every hour). Physical therapy can begin as soon as possible. Physical therapy is individualized but may include supported or unsupported walking, passive flexion and extension of the limbs, massage, or swimming. A daily record of physical therapy will ensure that this therapy is not overlooked and allows for multiple individuals, including the owner, to become involved in the healing process.

Massage and passive range of motion of the limbs is reasonable even in stuporous or comatose animals. Because severely impaired animals have little control over their movements, they may be predisposed to secondary musculoskeletal injuries. Cautious manipulation of comatose and stuporous animals is necessary to prevent iatrogenic injury. More rigorous physical therapy is begun when the animal is alert.

145.4 COMMON POSTOPERATIVE COMPLICATIONS

Postoperative complications following intracranial surgery include those involving damage or injury to the intracranial nervous system as well as systemic abnormalities. Iatrogenic injury to the brain often results in intracranial signs that are present immediately upon recovery from anesthesia or evolve within the following 48 to 72 hours. Intracranial hemorrhage, increasing cerebral edema, increasing ICP, and ischemia due to cerebrovascular disease are most often the causes of neurologic deterioration following surgery. As with all surgery, infectious complications are possible, but overall are rare.

Seizures are possible even if they were not present preoperatively.[40] Seizures that occur during the immediate postoperative period are managed in standard fashion. Intravenous diazepam boluses are used acutely if seizures occur. If the animal was receiving maintenance anticonvulsant medication before surgery, dosages are adjusted as necessary. If recurrent seizure activity ensues, a constant infusion of diazepam may be needed. In the animal that has not been receiving anticonvulsants, maintenance is initiated.[41] Seizures may suggest increasing ICP or poor cerebral perfusion and, if prolonged or severe, may warrant repeat evaluation with an intracranial imaging study.

With definitive surgical therapy, we have noted that some dogs seem overly sedated when receiving phenobarbital following surgery. This usually becomes most apparent between 2 and 5 days after surgery. Serum phenobarbital levels have not been elevated suggesting that, either because of alterations in brain blood flow or cellular concentration of the antiepileptic medication, the effects of phenobarbital may be relatively more potent after surgery. Seemingly excessive sedation from a similar dosage of phenobarbital may last for 3 to 5 days, but it usually is self-limiting. If the sedative effects are excessive, the phenobarbital dosage may need to be decreased for a few days.

Increasing ICP is a common complication following intracranial surgical manipulation. Increases in ICP may result from a variety of secondary pathophysiologic sequelae. Treatment to lower ICP is indicated when increases occur.

145.4.1 Treatment of Increased Intracranial Pressure

Treatment recommendations for increased ICP are taken primarily from those for management of general brain injury (Box 145-1; see Chapter 100, Intracranial Hypertension).

145.4.2 Nonneurologic Complications

As with all diseases, an understanding of the pathophysiology associated with the disease is necessary when determining the most appropriate treatment. Pathophysiologic alterations following intracranial surgery may occur for a variety of reasons. Their scope and severity may be influenced by the underlying type, extent, and severity of intracranial disease, iatrogenic brain injury during the surgical manipulations, as well as systemic health apart from that of the nervous system. Systemic pathophysiologic alterations such as changes in blood pressure, coagulation status, hydration, nutrition, and the function of other organ systems require general critical care assessment and treatment and are beyond the scope of this chapter. Appropriate and intensive critical care assessment and management are imperative, because many of the complications that occur in these animals do so during the immediate postoperative period.

145.4.2.1

Box 145-1 Treatment of Increased Intracranial Pressure

145.4.2.1.1

Therapies With Established Efficacy

IV, Intravenous.

- Fluid resuscitation with isotonic fluids
- Diuretics
- Mannitol (0.25 to 1 g/kg IV)

145.4.2.1.2

Therapies With Possible but Unknown Efficacy

- Hypertonic saline (3% solution, 5.3 ml/kg IV; 23.4% solution, 0.7 mg/kg IV)
- Head elevation
- Furosemide (0.07 to 1 mg/kg IV)
- Hyperventilation
- Cerebrospinal fluid aspiration
- Craniotomy

145.4.2.1.3

Miscellaneous Drugs

- Deferoxamine mesylate
- Superoxide dismutase
- Allopurinol
- Opiate antagonists (naloxone)

Thyrotropin-releasing hormone and calcium channel blockers

145.4.2.1.4 Therapy With Unknown Efficacy and Potential Detrimental Effects

Glucocorticoids

Of the nonneurologic complications following intracranial surgery, pneumonia is the most common.[45] Numerous factors may contribute to the development of pneumonia, but this is probably the result of aspiration of food or other digestive material. Megaesophagus seems to be a risk factor associated with pneumonia in dogs following intracranial surgery. Many of these dogs are also chronically ill and in overall debilitated states. Many dogs are receiving multiple drugs, including glucocorticoids and anticonvulsants. Glucocorticoids, because of their immunosuppressive and catabolic effects, may contribute to development of pneumonia. Often these dogs have dry mouths and oral disease that predisposes to alterations in the microorganisms in the mouth. Some dogs received perioperative or postoperative antibiotics, which could have altered the normal flora of the mouth and pharynx or predisposed to superinfection. Some animals, although apparently able to gag reflexively, may not be effectively swallowing accumulated saliva or food and water. Coughing may also be suppressed. Finally, early feeding before adequate swallowing probably plays a role. Although all of the causes of pneumonia have not been clarified, this complication has severe enough consequences to warrant concern.

A fever is usually a cardinal sign of pneumonia in these dogs. Any dog with a fever during the postoperative period should be evaluated with a thoracic radiograph. Although not ideal nutritionally, nothing orally for up to 5 days following surgery may be the best way to prevent pneumonia from developing in these animals. We have attempted to use various types of percutaneous alimentation including gastrostomy, nasogastric, esophagostomy, and jejunostomy tubes in these dogs without a significant decrease in the incidence of pneumonia. The most appropriate way to manage alimentation in these dogs has not been established.

145.5 SUGGESTED FURTHER READING*

RS Bagley: Intracranial pressure in dogs and cats: physiology and treatment. *Comp Cont Educ Pract Vet*. **18**, 1996, 605, *An overview of ICP considerations in animals*.

RS Bagley: Pathophysiologic sequelae of intracranial disease. *Vet Clin North Am Small Anim Pract*. **26**, 1996, 711, *An overview of pathophysiologic alterations associated with intracranial disease*.

JL Cornick: Anesthetic management of patients with neurologic abnormalities. *Comp Cont Educ Pract Vet*. **14**, 1992, 163, *A basic reference that discusses many of aspects of anesthesia in animals with intracranial abnormalities*.

* See the CD-ROM for a complete list of references

146 Chapter 146 Portosystemic Shunt Management

Margo Mehl, DVM, DACVS

146.1 KEY POINTS

- Clinical signs of portosystemic shunt (PSS) include neurologic, gastrointestinal, and urinary abnormalities, and can manifest as other signs such as prolonged recovery from anesthesia.
- Intrahepatic PSS is more common in large breed dogs and extrahepatic PSS usually occurs in small dogs and cats.
- The goal of preoperative PSS stabilization and medical treatment is to control clinical signs of hepatic encephalopathy and prevent progression of neurologic signs.
- The treatment of choice is surgical attenuation of the shunting vessel.
- Perioperative morbidity and mortality is higher with intrahepatic PSS repair than with surgical correction of extrahepatic PSS.
- Serious postoperative complications of PSS include hemorrhage, hypoglycemia, seizures, and portal hypertension.
- Several predictors of clinical outcome have been identified for surgical management of extrahepatic and intrahepatic PSS in dogs.

146.2 INTRODUCTION

Portosystemic shunts (PSSs) are vascular anomalies that connect the portal circulation with the systemic circulation, diverting portal blood away from the liver. These vascular anomalies are categorized most commonly as extrahepatic or intrahepatic shunts. Extrahepatic PSSs can be further categorized as congenital or acquired and often are described based on the supplying and draining vessels, such as *portocaval* or *portoazygos shunts*. Intrahepatic PSSs usually are classified based on the branch of the portal vein supplying the shunt and divide intrahepatic PSSs into left-divisional, central-divisional, and right-divisional categories.

Single extrahepatic PSSs are the most commonly reported type in dogs and cats; they are congenital and seen primarily in small breed dogs.[1-3] Clinical signs are related to hepatic dysfunction, including gastrointestinal (GI) signs, central nervous system (CNS) disturbances, and urolithiasis. Some patients will require intensive therapy to stabilize them before surgical correction of the PSS. Postoperative complications can occur in an unpredictable and precipitous manner and can range in severity from ascites to life-threatening hemodynamic and neurologic abnormalities, making these patients extremely challenging to treat after surgery.

146.3 PREOPERATIVE STABILIZATION

Animals with PSS commonly will have neurologic abnormalities, GI signs, urinary signs, and other signs such as prolonged recovery from a previous anesthesia.[3] Preoperative stabilization depends on the animal's status on arrival and often includes fluid therapy and anticonvulsant medications to stop the progression of neurologic signs. If a patient has mild clinical signs of hepatic encephalopathy and is stable, medical treatment may be initiated (i.e., low-protein diet, anticonvulsants, antibiotics, and cathartics).

On the other hand, if a patient has moderate to severe signs of hepatic encephalopathy, more aggressive therapy is indicated. A major contributing factor to worsening hepatic encephalopathy is hemorrhage into the GI tract, which acts as a large protein source for further ammonia production. To reduce signs of hepatic encephalopathy, immediate removal of any protein source within the GI tract with lactulose enemas is a priority. Ongoing ammonia production and absorption should be prevented with oral antibiotics and cathartics (see Chapter 103, Hepatoencephalopathy).

GI signs in patients with PSS often include vomiting and diarrhea, which can lead to fluid and electrolyte imbalances. These imbalances should be addressed before surgical correction of the PSS. Pica is reported frequently in PSS patients, and as a result the patient may be vomiting secondary to a GI foreign body.

Occasionally animals can have a urinary emergency secondary to PSS, such as a urethral obstruction. Initial treatment may include correcting fluid and electrolyte abnormalities followed by relief of the obstruction.

146.4 MEDICAL MANAGEMENT

As long as portal blood flow is being shunted away from the liver, hepatic function will continue to decline. Surgery offers the opportunity to redirect portal blood back to the liver. Medical management should be initiated before surgical correction of the PSS in animals with signs of hepatic encephalopathy, and anticonvulsant therapy may be beneficial in PSS patients preoperatively. The benefit of preoperative anticonvulsant therapy was evaluated by Tisdall and others[4] and showed that prophylactic anticonvulsants did not significantly reduce the risk of postoperative neurologic signs, but may have reduced their severity. Therefore routine use of prophylactic anticonvulsant therapy in all dogs with PSS may be warranted. There are several protocols for preoperative anticonvulsant therapy and the authors' recommendation in dogs is potassium bromide at a loading dosage for 24 hours (100 mg/kg PO q6h) or a maintenance dosage for a minimum of 2 weeks (40 mg/kg PO q24h) (Table 146-1).

Table 146-1 Suggested Preoperative Anticonvulsant Therapy in Dogs and Cats With PSSs

Drug	Canine and Feline Dosage	Therapeutic Blood Levels
Phenobarbital	1 to 2 mg/kg PO q12h	15 to 45 µg/ml
Potassium bromide	Loading dosage*: 100 mg/kg PO q6h × 4 doses (total dosage of 400 mg/kg in 24 hr) Maintenance dosage: 60 to 100 (canine) mg/kg once a day	2 to 3 mg/ml when used as a sole agent 1 to 2 mg/ml when used in conjunction with phenobarbital

From Plumb DC. *Plumb's veterinary drug handbook*, ed 5, Stockholm, 2005. PharmaVet Inc.

*A loading dose is recommended if therapeutic levels are required quickly. This is one of several protocols for potassium bromide loading. A maintenance dose given longer than 15 days in dogs will provide adequate blood levels as an alternative to giving the loading dose.[22] These drugs can be associated with neurologic and respiratory depression and patients should be monitored accordingly. Loading doses of potassium bromide can cause gastrointestinal disturbances.

PO, Per os, *PSSs,* portosystemic shunts.

Feline patients with PSS have a high incidence of neurologic complications after surgery,[5,6] so preoperative anticonvulsant therapy is often instituted. Potassium bromide has been associated with allergic airway disease in cats; consequently the author uses phenobarbital (1 to 2 mg/kg PO q12h) and recommends confirming that the serum concentrations reach therapeutic levels before surgery (see Table 146-1). Because phenobarbital is metabolized in the liver, animals with liver insufficiency may require lower dosages to achieve therapeutic levels.

The goal of medical therapy is to decrease production and absorption of ammonia, and management includes dietary modification, antibiotic therapy, and cathartics. Typically, a diet high in carbohydrates and low in protein will decrease the building blocks for ammonia production. Dairy and vegetable protein sources are less likely to cause signs of hepatic encephalopathy than are meat proteins. Antibiotics that concentrate in the GI tract, such as amoxicillin, neomycin, and metronidazole, will reduce the number of bacteria responsible for ammonia production. Cathartics, such as lactulose, will shorten the transit time in the GI tract and trap ammonium ions in the lumen, reducing its absorption. Acid-base imbalances, electrolyte abnormalities, and hypoglycemia should be identified and corrected before surgery.

Hypoalbuminemia is a consistent finding in patients with PSSs. Because their hypoalbuminemia is chronic, it generally is not associated with signs in the stable patient and as such it does not warrant therapy. It will, however, be a concern in the patient that requires significant fluid resuscitation, a common requirement of the preoperative PSS patient. Large volumes of crystalloid fluid will cause hemodilution and worsen the hypoalbuminemia, making maintenance of intravascular volume very difficult.

Hemodynamically compromised hypoproteinemic patients generally require support of serum colloid osmotic pressure (COP). Although synthetic colloids such as hetastarch are very effective at increasing COP, they interfere with coagulation. Because patients with PSSs tend to have coagulation deficits,[7] synthetic colloids should be avoided or minimized. Plasma transfusions will support intravascular volume, help maintain COP, and provide coagulation factors. For this reason plasma can be an invaluable therapy in the perioperative stabilization of the patient with a PSS.

146.5 SURGICAL OPTIONS

The treatment of choice is surgical attenuation of the shunting vessel.[1] The traditional surgical technique involves placing a ligature around the anomalous vessel, which is gradually tightened while measuring portal pressure and observing the splanchnic viscera. If the ligature is too tight, there is significant risk of inducing portal hypertension, which is a severe and often fatal complication. Criteria for judging the safe degree of PSS attenuation include an increase in portal pressure with temporary complete PSS attenuation of no more than 10 cm H_2O.[8-11]

Gradual, rather than acute, PSS occlusion has been advocated as a safer surgical technique.[12,13] It is proposed that gradual occlusion allows the development of the hepatic architecture in response to the increased vascular supply, meanwhile avoiding fatal portal hypertension. The ameroid ring constrictor and the cellophane band are both designed to produce gradual vascular occlusion.

Surgical access, localization, and attenuation of an intrahepatic PSS can be challenging. A number of techniques, both intravascular and extravascular, have been reported for accessing an intrahepatic PSS, some of which require a caudal sternotomy. Intrahepatic PSSs are often large vessels shunting sizeable volumes of portal blood away from the liver, and there is a significant risk of creating portal hypertension with excessive attenuation. Therefore most patients with an intrahepatic PSS will tolerate only partial PSS ligation.

146.6 POSTOPERATIVE MONITORING

General critical care principles apply to the postoperative management of patients with PSSs, and close observation is extremely important because their status can deteriorate rapidly. Optimal outcome occurs when clinicians identify life-threatening complications early and treat them aggressively.

Several parameters should be monitored in these patients after surgery, including arterial blood pressure and heart and respiratory rates. These patients are often young, small breed dogs that can be hypothermic after surgery and benefit from continuous temperature monitoring and active rewarming. Box 146-1 provides a comprehensive list of parameters for postoperative monitoring.

Hypovolemia is a common postoperative issue as a result of venous congestion of the splanchnic viscera, GI losses, and hypoproteinemia, which may be more severe following intraoperative hemodilution. Clinical signs of hemodynamic compromise such as evidence of poor perfusion or systemic hypotension should be considered results of hypovolemia unless proven otherwise. Central venous pressure monitoring may be advantageous to guide fluid therapy. When choosing a fluid for volume resuscitation, it is important to consider that these patients will have both a low COP and coagulation defects. As a result, plasma is often the fluid of choice in combination with isotonic crystalloids.

146.6.1 Box 146-1 Recommended Clinicopathologic Parameters to Monitor in the Postoperative PSS Patient

146.6.1.1 Clinical Parameters

*When direct arterial pressure is unavailable, indirect arterial pressure should be measured. *PSS,* Portosystemic shunt.

- Heart rate
- Respiratory rate
- Temperature
- Direct arterial pressure*
- Central venous pressure
- Electrocardiogram
- Urine output
- Abdominal circumference

Intraabdominal pressure

Mentation and neurologic status

146.6.1.2 Laboratory Parameters

Packed cell volume

Total protein

Glucose

Lactate

Electrolytes

Acid-base status

Monitoring intraabdominal pressure with a urinary catheter can provide useful information and help detect life-threatening portal hypertension (see Chapter 206, Intraabdominal pressure). Clinicopathologic parameters to evaluate at regular intervals after surgery include packed cell volume, total protein, lactate, glucose, and electrolytes (Box 146-1). Severity and progression of abdominal distention can be monitored with serial measurements of abdominal circumference using a measuring tape or string. These patients may require a continuous electrocardiogram to detect cardiac arrhythmias. Tachycardia is frequently the first sign of hypovolemia in these patients.

146.7 POSTOPERATIVE COMPLICATIONS

The three most important postoperative complications seen in patients with PSSs are portal hypertension, coagulopathy, and neurologic abnormalities. Portal hypertension occurs when the liver is unable to accommodate the increase in portal blood flow after closure of the shunting vessel. This leads to venous congestion of the abdominal organs normally drained by the portal system, which is associated with hemodynamic compromise. Signs of portal hypertension are abdominal pain, abdominal distention, melena, diarrhea, and systemic hypotension. The degree of portal hypertension can vary from minor to moderate to severe. Most cases with minor to moderate portal hypertension will respond to fluid therapy, including blood products, and opioid-based pain management. Animals with severe portal hypertension that is not responsive to aggressive medical therapy may require emergency surgery to remove the occlusive device from the shunting vessel.

The portal vein supplies the liver with 50% of its oxygen requirements and other essential hepatotrophic factors.[3] In patients with PSSs, portal venous blood is bypassing the liver, resulting in reduced hepatic mass and decreased production and activation of coagulation factors.[7] Therefore these patients often have abnormal coagulation and require plasma and other blood products both during surgery and postoperatively. Clinical signs of coagulopathy can range from minor oozing from catheter and surgical sites to life-threatening hemorrhage into body cavities (see Chapter 66, Transfusion Medicine).

Table 146-2 Recommended Treatment for Neurologic Dysfunction in Patients With PSSs

Agent	Mode of Administration	Canine and Feline Dosage
Diazepam	Bolus	0.2 to 2 mg/kg IV to effect
	CRI	0.2 to 0.6 mg/kg/hr IV to effect
Midazolam	Bolus	0.1 to 0.5 mg/kg IV to effect
	CRI	0.1 to 0.3 mg/kg/hr IV to effect
Propofol	Bolus	2 to 6 mg/kg IV to effect
	CRI	0.1 to 0.6 mg/kg/min IV to effect
Phenobarbital	Bolus	2 to 5 mg/kg IV, can repeat at 20-min intervals up to a total dosage of 20 mg/kg
	Maintenance	2 to 4 mg/kg IV q12h
Pentobarbital	Bolus	3 to 15 mg/kg IV SLOWLY to effect
	CRI	0.5 to 5 mg/kg/hr to effect

From Plumb DC. *Plumb's veterinary drug handbook*, ed 5, Stockholm, 2005. PharmaVet Inc.

Note: All of these drugs are associated with moderate to profound neurologic and respiratory depression. Intensive monitoring is essential; patients may require intubation and mechanical ventilation.

CRI, Constant rate infusion; *IV,* intravenous; *PSSs,* portosystemic shunts.

Seizures can occur during the immediate postoperative period and have been reported up to 72 hours after surgery.[14] In some dogs, neurologic signs such as vocalization, disorientation, and ataxia are observed before seizures occur. Mild signs of partial seizures, such as disorientation, vocalization, salivation, or twitching, may resolve after administration of anticonvulsant therapy, whereas postoperative grand mal seizures are associated with a high mortality rate.[15,16] Management recommendations include preventing hypoglycemia and other electrolyte abnormalities and treating seizure activity early. There are several recommendations for treating seizure activity after surgical intervention for PSS in dogs, including a single agent or a combination of the following intravenous agents: diazepam, phenobarbital, pentobarbital, and propofol (Table 146-2). Anticonvulsant therapy protocols in PSS patients have not been evaluated scientifically, so there is not proven benefit of one agent (or agents) over another.

Controversy exists regarding what toxins are responsible for hepatic encephalopathy. It has been suggested that benzodiazepine receptor ligands play a role in the pathogenesis of hepatic encephalopathy; unfortunately the impact this has on the administration of exogenous benzodiazepines to patients with PSSs remains undetermined.[17,18] Numerous benefits and risks are associated with anticonvulsant drugs in patients with neurologic signs after surgery. It has been suggested that propofol stops seizure activity seen in the clinical patient but may not alter the electrical activity occurring in the brain. The impact this may have on the use of propofol in patients with postoperative neurologic dysfunction remains unclear. Postoperatively, dogs and cats with neurologic signs of partial or focal seizures should be treated aggressively to prevent the progression of clinical signs to grand mal seizures, which carry a grave prognosis.

It is important to remember that many of these therapies can cause loss of the gag reflex, hypoventilation, and apnea, which may necessitate intubation and mechanical ventilation. Inadequate airway protection can lead to aspiration pneumonia, which can have life-threatening consequences. Elevation of the partial pressure of carbon dioxide that occurs with hypoventilation is associated with cerebral vasodilation, leading to increases in intracranial pressure. This can be catastrophic in the patient with preexisting neurologic disease such as hepatic encephalopathy.

146.8 PROGNOSIS

A number of studies have reported the mortality rate associated with surgical repair of both extrahepatic and intrahepatic PSSs. The perioperative mortality rate for extrahepatic PSS repaired with a method for slow attenuation, cellophane banding, or ameroid ring constrictor placement has been reported to be between 5.5% and 7.1%.[18,19] Several factors that predict surgical mortality in dogs with a single extrahepatic PSS treated by ameroid ring constrictor placement are postoperative complications and preoperative white blood cell count.[18]

Similarly, the mortality rate and predictive factors for surgical mortality have been reported after surgical management of intrahepatic PSS. Papazoglou and others[20] reported a surgical mortality rate of 12.5% in 32 dogs with intrahepatic PSS repair, and several predictors for short-term outcome for dogs with intrahepatic PSS included body weight, total protein, albumin, and blood urea nitrogen concentrations. A number of studies have reported higher surgical mortality rates for intrahepatic PSS than for extrahepatic PSS. Because intrahepatic PSSs are often larger vessels shunting a substantial amount of portal blood around the liver, these patients are unlikely to live a normal lifespan without surgical intervention.

146.9 SUGGESTED FURTHER READING*

ML Mehl, AE Kyles, EM Hardie, et al.: Evaluation of ameroid ring constrictors for treatment for single extrahepatic portosystemic shunts in dogs: 168 cases (1995-2001). *J Am Vet Med Assoc*. **226**, 2005, 2020, *A retrospective paper that identified predictive factors for postoperative death, continued shunting, and long-term outcome*.

LG Papzoglou, E Monnet, HB Seim, II: Survival and prognostic indicators for dogs with intrahepatic portosystemic shunts: 32 cases (1990-2000). *Vet Surg*. **31**, 2002, 561, *A retrospective study evaluating predictive factors for long-term outcome in dogs with intrahepatic PSS and that determined PCV and TP were predictive for long-term survival*.

TM Tobias: Portosystemic shunts and other hepatic vascular anomalies. In DH Slatter (Ed.): *Textbook of small animal surgery*. ed 3, 2003, Saunders, Philadelphia, *A good review of hepatic vascular anatomy and embryonic development of the portal system. This chapter also provides a general overview of PSS diagnosis and treatment*.

* See the CD-ROM for a complete list of references

147 Chapter 147 Peritoneal Drainage Techniques

Matthew W. Beal, DVM, DACVECC

147.1 KEY POINTS

- A variety of medical and surgical disease processes necessitate the evacuation of fluid from the peritoneal cavity.
- When combined with source control, peritoneal drainage is a critical component in the management of chemical and septic peritonitis.
- Peritoneal drainage techniques may be used to facilitate preoperative stabilization of the patient with life-threatening hyperkalemia and azotemia secondary to urinary tract disruption.
- The peritoneal cavity may be drained initially using needle abdominocentesis or catheter abdominocentesis. When sustained drainage is indicated, a peritoneal dialysis catheter, closed suction drain, or open peritoneal drainage is employed.

147.2 INTRODUCTION

Sampling and evacuation of fluid from the peritoneal cavity is a cornerstone of both the diagnostic workup and various therapeutic strategies for the treatment of the dog or cat with an acute condition of the abdomen and a host of other medically and surgically managed disease processes. A number of medical and surgical procedures may be used to facilitate peritoneal drainage and each has specific indications, contraindications, advantages, and disadvantages. A thorough knowledge of peritoneal drainage strategies allows for appropriate medical and surgical decision making and will maximize the likelihood of a positive clinical outcome.

147.3 INDICATIONS FOR PERITONEAL DRAINAGE

147.3.1 Septic Peritonitis

Septic peritonitis is by far the most common indication for sustained peritoneal drainage. It is generally accepted that the removal of fluid that may contain infectious agents, inflammatory mediators, and foreign material (e.g., bile, ingesta) is beneficial to resolution of the infection within the peritoneal space. Furthermore, fluid within an infected cavity may significantly impair humoral and cell-mediated immune mechanisms.[1] Despite a lack of prospective, randomized controlled studies in dogs and cats to definitively document decreased morbidity and improved outcome when peritoneal drainage is established, open peritoneal drainage (OPD) or closed suction peritoneal drainage (CSD) is the standard of care for generalized septic peritonitis.

Recommendations for abdominal drainage techniques in dogs and cats with septic peritonitis may be found in Box 147-1. In clinical practice, the author prefers to use CSD, even when criteria are met for primary closure. CSD allows not only for drainage of abdominal fluid that may accumulate but also for sampling of the abdominal fluid for cytologic analysis and confirmation that the inflammatory reaction and infectious process are indeed subsiding. Detailed descriptions of OPD and CSD techniques may be found later in this chapter.

147.3.1.1 Box 147-1 Guidelines for Abdominal Drainage in Dogs and Cats With Septic Peritonitis

147.3.1.1.1 Open Peritoneal Drainage

Source control accomplished

Severe generalized peritonitis

Severe contamination that cannot be resolved completely with debridement and lavage

147.3.1.1.2 Closed Suction Drainage

Source control accomplished

Moderate to severe generalized peritonitis

Localized peritonitis

Contamination that can be resolved through debridement and lavage

147.3.1.1.3 Primary Closure

Source control accomplished

Local or focal peritonitis of nongastrointestinal origin

Minimal contamination that is resolved completely with debridement and lavage

147.3.2 Chemical Peritonitis

Uroperitoneum and bile peritonitis account for two common sources of chemical peritonitis. Although most commonly sterile, both conditions may be associated with sepsis. Cytologic examination and biochemical analysis (glucose and lactate) of abdominal fluids may aid in differentiating between sterile and septic processes. (Please see the preceding section for a discussion of abdominal drainage in dogs and cats with septic peritonitis.)

Bile peritonitis is associated with an intense inflammatory response. Bile salts are toxic to mesothelial cells in the peritoneal cavity, and the presence of bile alters host defense mechanisms and may reduce phagocytic abilities of inflammatory cells in the peritoneal space.[2-3] OPD is probably unnecessary in sterile bile peritonitis and may predispose to nosocomial colonization of the peritoneal cavity. The author has found CSD to be valuable for maintaining peritoneal cavity decompression and facilitating ongoing removal of small bile particulate matter in dogs with sterile bile peritonitis.

147.3.2.1

Box 147-2 Possible Indications for Peritoneal Drainage

- Septic peritonitis
- Bile peritonitis
- Uroperitoneum
- Pancreatitis-associated peritonitis
- Peritoneal dialysis
- Increased intraabdominal pressure
- Abdominal effusion compromising ventilation
- Abdominal effusion compromising patient comfort

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Peritoneal drainage plays important roles in both the preoperative and postoperative management of the dog or cat with uroperitoneum. In the preoperative setting, in addition to standard therapeutic measures to manage hypovolemia and hyperkalemia (see Chapters 55 and 137, Potassium Disorders and Hemodialysis and Peritoneal Dialysis, respectively), a peritoneal dialysis catheter or other fenestrated catheter in the peritoneal space will facilitate the evacuation of urine from the peritoneal cavity and the diversion of urine that continues to leak from the disrupted urinary tract until the patient is stable and surgical intervention can be performed. In the postoperative setting, because the likelihood of large particulate debris in the peritoneal space concurrent with uroperitoneum is unlikely, CSD (rather than OPD) will facilitate the evacuation of inflammatory exudates from the peritoneal cavity and should be necessary for only 1 to 3 days postoperatively in dogs and cats with moderate to severe generalized peritonitis.

147.3.3

Other Indications for Peritoneal Drainage

Reliable cannulae for infusion and drainage of fluid from the peritoneal space are critical to the practice of peritoneal dialysis. Two CSD catheters or other long-term peritoneal dialysis catheters may be placed laparoscopically or through a small laparotomy incision. Renal biopsy might be performed during the procedure (see Chapter 137, Hemodialysis and Peritoneal Dialysis).

Increased intraabdominal pressure has been documented in conditions including, but not limited to, portal hypertension, repair of chronic diaphragmatic hernia, abdominal counterpressure bandages, hemoperitoneum, and gastric dilatation-volvulus.[4] Elevated intraabdominal pressure has generalized deleterious effects on the cardiovascular system, primarily mediated through decreased venous return and subsequent decreases in cardiac output. Local cardiovascular effects include decreased end-organ perfusion, both dependent and independent of the aforementioned effect on cardiac output. Increased intraabdominal pressure is also transmitted to the thoracic cavity via the diaphragm and may result in hypoxemia and hypoventilation. Peritoneal drainage may be indicated for animals with intraabdominal pressures higher than 30 cm H_2O as measured with transurethral techniques.[4] Box 147-2 lists conditions for which peritoneal drainage might be employed. Routine drainage of peritoneal fluid accumulations due to right heart failure, liver disease, or other noninflammatory or noninfectious processes is not indicated in the absence of increased intraabdominal pressure or respiratory embarrassment.*

* 10.2 Fr 30-cm Polyurethane Thoracic Drainage Catheter, SurgiVet, Waukesha, WI 53186.

147.4 TECHNIQUES FOR PERITONEAL DRAINAGE

147.4.1 Needle or Catheter Abdominocentesis

Abdominal drainage via a hypodermic needle or over-the-needle catheter is a minimally invasive technique. However, it is very inefficient and does not allow for sustained abdominal drainage. Additionally, clogging of the needle or catheter with omentum or other visceral structures may preclude effective evacuation. This technique is more useful for sampling of abdominal fluid for diagnostic purposes or one-time decompression in a patient exhibiting signs of respiratory compromise or discomfort secondary to abdominal fluid accumulation.

Necessary supplies include an 18- to 20-gauge hypodermic needle or over-the-needle catheter of a length appropriate for the anticipated thickness of the body wall. If an over-the-needle catheter is used, a small 1- to 3-mm side hole may be created using a No. 11 scalpel blade approximately one fourth of the way from the tip of the catheter to the hub. The side hole increases the surface area for the retrieval of fluid and makes occlusion of the catheter with omentum less of a problem. Additional equipment will include a 60-cc syringe, three-way stopcock, and intravenous extension tubing to attach to the needle or catheter. The author prefers to use a closed collection system to minimize the likelihood of contamination of the peritoneal cavity and to minimize the introduction of air into the peritoneal space.

The patient is positioned in left lateral recumbency to allow the spleen to fall away from the proposed site of needle insertion. The abdomen should be liberally clipped of hair and aseptically prepared as if for a surgical procedure and draped using a fenestrated paper or cloth drape. The proposed insertion site is located 2 to 3 cm caudal to the umbilicus, either on or slightly to the left of midline. Local infusion of lidocaine hydrochloride may decrease patient discomfort if drainage is likely to take an extended time. The needle should be inserted perpendicular to the surface of the body and advanced through the skin. The stopcock may then be opened and the syringe aspirated. The needle is then advanced in 1- to 2-mm increments and the syringe aspirated intermittently until fluid is retrieved. In circumstances in which only a small volume of peritoneal fluid is present, four-quadrant abdominocentesis may be performed. Ultrasonography may be used to guide the sampling needle to very small-volume fluid accumulations. Samples should always be saved for cytologic analysis, culture (if indicated), and chemical analysis, if indicated (see Chapter 155, Abdominocentesis)†.

† Lidocaine HCl Injectable 2%, AmTech Group, Phoenix Scientific, St. Joseph, MO 64503.

147.4.2 Paracentesis With a Fenestrated Catheter per the Mini-Laparotomy Method

In contrast to abdominocentesis with a needle or over-the-needle catheter, use of a catheter with multiple fenestrations will facilitate both rapid and sustained decompression of larger volume abdominal effusions (mini-laparotomy method). This technique might be used during stabilization of a dog with bladder rupture and uroperitoneum in preparation for surgical intervention. 639 640

A number of commercially available catheters may be used.* Many of these are designed to be placed via a completely closed method using a trochar within the catheter; however, it is the author's experience and recommendation that placing these catheters using a small laparotomy incision will optimize the likelihood of successful placement, as well as minimizing risk of injury to intraabdominal organs that may occur during closed placement.

The patient should be given sedatives and analgesics appropriate for the cardiovascular and respiratory status. First, the bladder should be emptied via catheterization or gentle expression. The patient should be prepared as described previously (Needle or Catheter Abdominocentesis). Local anesthesia techniques focusing on the skin, subcutaneous tissues, and the body wall are critical to performing this procedure with a minimum of discomfort to the patient.

Strict asepsis must be practiced. The patient should be placed in dorsal recumbency, and a 1- to 2-cm skin incision should be made on the ventral midline approximately 2 cm caudal to the umbilicus. Blunt dissection to the linea alba should be performed using a hemostat. The linea should be grasped at both ends of the incision using hemostats allowing for the creation of tension and elevation of the No. 11 scalpel blade, a 3- to 4-mm incision should be created in the linea. The catheter should be placed through a separate skin incision 2 cm lateral to the insertion site. This creates a small subcutaneous tunnel, making the collection system less susceptible to contamination. When using this technique in the postoperative setting, the catheter should never be inserted through the laparotomy incision. If the catheter is of a type in which the trochar protrudes from the tip of the catheter, it should be withdrawn to just inside the catheter. The trochar and catheter may then be inserted into the peritoneal cavity in a dorsocaudal direction (toward the pelvic inlet). After the trochar and catheter are 2 to 3 cm inside the peritoneal cavity, the catheter may be advanced over the trochar. Dead space in the subcutaneous tissues should be eliminated and the skin incision closed routinely. A purse-string and finger-trap suture should be used to secure the catheter to the body wall. A sterile dressing should be applied and changed as needed.

[*] 10.2 Fr 30-cm Polyurethane Thoracic Drainage Catheter, SurgiVet, Waukesha, WI 53186.

147.4.3 Paracentesis With a Fenestrated Catheter Using the Seldinger Technique

Abdominal paracentesis may also be performed using a fenestrated catheter placed via the Seldinger technique.[†] The patient should be sedated and prepared as described previously, positioned in dorsal recumbency, and the urinary bladder evacuated. Landmarks are similar to those described earlier or slightly off of midline to avoid the round ligament of the bladder. Local anesthetic usage will facilitate this procedure (see Chapter 63, Central Venous Catheterization). Once in place, the catheter may be secured and dressed as described in the previous paragraph (Paracentesis With a Fenestrated Catheter per the Mini-Laparotomy Method).

[†] Tenckhoff Acute Peritoneal Dialysis Catheters, Cook Medical, Bloomington, IN 47402–4195.

147.4.4 Surgical Placement of Closed Suction Drains

CSD has allowed surgeons to find a middle ground between the sometimes risky method of primary closure of the abdominal cavity and the labor-intensive method of providing OPD in the patient with acute, effusive, surgically treated abdominal disease (e.g., septic peritonitis).[5] The author also uses closed suction drains via a limited laparotomy incision for peritoneal dialysis.

Numerous types of closed suction drains exist, ranging from flat drains with multiple fenestrations to those that are fluted (Color Plate 147-1), a design that is resistant to obstruction by omentum, tissue, and cellular debris. Closed suction drains are placed as the last step before abdominal closure. In a cat or small dog, a single 10-Fr drain may be placed in a craniocaudal direction. In larger dogs, dual 10- or 15-Fr drains may be placed parallel to one another in a craniocaudal direction, or with one drain located cranially and the other located more caudal. The drains may exit the skin 2 to 3 cm off of midline.

Some drains come swaged onto a steel trochar that is used to pass the drain tubing from the intraabdominal space to the drain exit site. The drains should never exit from the laparotomy incision. They should be secured with a purse-string suture at the exit point and continued into a finger-trap pattern. Once the abdomen is closed, the drains should be connected to the negative pressure reservoir(s) with antireflux valve(s).[‡] The drain exit sites should be covered with sterile dressings and an abdominal bandage. The negative pressure reservoir may then be attached to the abdominal bandage. The sterile dressing and abdominal bandage should be replaced daily and the ostomy site and surgical incision evaluated for evidence of infection.

Drain reservoirs should be evacuated when they are full. Drain effluent should be evaluated daily or every 48 hours to ensure that the underlying disease process is resolving. The author prefers to collect these samples for cytologic analysis from the drain tubing rather than the reservoir. Routine precautions to prevent contamination of the drain tubing or reservoir should be performed. The drains may be removed when the drainage declines to acceptable levels (5 to 7 ml/kg q24h), patient condition is improving, and cytologic characteristics of the drain fluid show a resolving inflammatory response and no evidence of infection. The presence of indwelling drains certainly places the patient at risk for hospital-acquired infection, but this hazard may be prevented by strict attention to aseptic technique while handling the drains and while changing the dressings.

When closed suction drains are used to perform peritoneal dialysis, one drain may be used for infusion and a second for drainage, or the drain tubing may be connected using a Y adaptor that allows both drains to be used for infusion and drainage (see Chapter 137, Hemodialysis and Peritoneal Dialysis).

[‡] J-Vac, Johnson & Johnson Medical, Somerville, NJ 08876.

147.4.5 Open Peritoneal Drainage Technique

OPD was the original alternative to primary closure in patients with septic peritonitis.[6, 7] Once source control has been established and the abdominal cavity lavaged thoroughly, the OPD technique may be performed. In male dogs, the parapreputial aspect of the ventral midline incision is closed routinely. A urinary catheter should be placed in all dogs to prevent urine from soiling the abdominal bandage and to help quantify urine output. The technique for providing OPD involves placement of a monofilament suture (most often 2-0 or 0 polypropylene) in the external rectus sheath as is routine for closure of a ventral midline abdominal incision. However, the sutures are not pulled tight, leaving a gap for drainage of approximately 2 to 4 cm. Sutures prevent evisceration during bandage changes (Color Plate 147-2). A sterile, nonadherent dressing[*] is then placed over the abdominal incision. This is followed by a large layer of highly absorbent sterile dressing[†] and a sterile hand towel. The entire bandage is secured using cast padding,[‡] stretchable roll gauze,[¶] and additional bandaging materials as needed. The external bandage material should extend far cranial and caudal to the abdominal incision to ensure that it will remain covered in the event of bandage migration.

The abdominal dressing should be changed a minimum of 1 to 2 times daily and always when strike-through is evident. Weighing the abdominal dressing before placement and after removal may help quantify fluid losses and thus help direct fluid therapy. During bandage change, sterile-gloved fingers may be inserted into the abdominal cavity between sutures to ensure that fibrin and abdominal organs are not precluding effective abdominal drainage. Abdominal fluid should be evaluated daily or every 48 hours.

Once abdominal drainage has decreased and cytologic characteristics of the drainage fluid show evidence of resolving inflammatory response and no evidence of infection, the abdomen may be closed. The author advocates reexploration and lavage of the abdomen at the time of closure. Aerobic and anaerobic cultures may be collected from the abdominal cavity. The subcutaneous and skin layers are debrided as needed, lavaged, and closed routinely. OPD may place the patient at risk for hospital-acquired infection, but this hazard may be prevented by strict attention to aseptic technique while performing dressing changes and handling the drainage system.

* Adaptic, Johnson & Johnson Medical, Gargrave, Skipton, UK, BD23 3RX.

† STERIROLL, Franklin-Williams, Lexington, KY. 40502

‡ Specialist Cast Padding, BSN Medical, Brierfield, England BB9 SNJ.

¶ Conform Stretch Bandages, Kendall, Mansfield, MA 02048.

147.5 COMPLICATIONS OF PERITONEAL DRAINAGE

147.5.1 Volume and Albumin Loss and Peritoneal Drainage Techniques

All surgical procedures have inherent disadvantages and complications. A knowledge and expectation of certain complications inherent to peritoneal drainage techniques will allow the clinician to anticipate and modulate these. Anytime the peritoneum is evacuated of fluid, there will be volume loss as well as potential loss of albumin and other proteins. Appreciation that abdominal fluid is in flux with the extracellular fluid volume and that significant volumes of fluid can be lost as a result of ongoing drainage will allow the clinician to replace fluid volumes and provide oncotic support as necessary.

One advantage of the CSD technique is easy quantification of volume loss. Comparing the weight of the dry OPD bandage with its weight after removal can give an estimate of fluid losses through the OPD site. Close attention should be paid to total volume losses as well as patient albumin concentration, colloid oncotic pressure, and evidence of peripheral edema when choosing a fluid therapy regimen. Early nutritional support should be strongly considered in patients with acute abdominal illness.

147.6 CONCLUSION

A variety of peritoneal drainage techniques are available to allow clinicians to provide one-time, intermittent, or sustained drainage for patients requiring evacuation of fluid from the peritoneal cavity. Attention to indications, contraindications, and aseptic technique will allow these techniques to be employed with minimal complications.

147.7 SUGGESTED FURTHER READING*

MG Conzemius, JL Sammarco, DE Holt, et al.: Clinical determination of preoperative and postoperative intra-abdominal pressures in dogs. *Vet Surg*. **24**, 1995, 195, *An excellent prospective evaluation of the effects of elective surgical procedures and clinical disease states associated with abdominal distention on intraabdominal pressure. Transurethral technique for measuring intraabdominal pressure described.*

MG Mueller, LL Ludwig, LJ Barton: Use of closed-suction drains to treat generalized peritonitis in dogs and cats: 40 cases (1997-1999). *J Am Vet Med Assoc*. **219**, 2001, 789, *The only veterinary study detailing a case series of dogs and cats with septic peritonitis in which closed suction drains were used to maintain abdominal decompression during the postoperative period. Describes technique for CSD placement. Descriptive only, limited by its retrospective nature.*

* See the CD-ROM for a complete list of references

148 Chapter 148 Postthoracotomy Management

Eric Monnet, DVM, PhD, DACVS, DECVS

148.1 KEY POINTS

- Postoperative management of the patient after thoracotomy requires intensive monitoring of pulmonary and cardiovascular function.
- Optimization of oxygen delivery is the primary goal during the postoperative period.
- Hypoxemia, hypotension, and arrhythmias are very common after thoracotomy.
- Aggressive pain control to improve comfort and ventilation is essential.

148.2 INTRODUCTION

Thoracotomy is a common surgical procedure performed to manage cardiac conditions, lung pathology, pleural effusion of various origins, esophageal disease, and mediastinal disease. Intercostal thoracotomy and median sternotomy are the most common approaches used in veterinary medicine. Penetration of the pleural space induces tremendous changes in pulmonary and cardiovascular physiology that can impact patient recovery. These patients require intensive monitoring with an emphasis on evaluation of pulmonary function and hemodynamics.

148.3 PHYSIOLOGIC EFFECTS OF THORACOTOMY

Opening the thoracic cavity results in disruption of the subatmospheric pleural pressure. Consequently lung collapse occurs (atelectasis) and venous return is impaired, compromising cardiac output.[1-3]

148.3.1 Atelectasis

Loss of subatmospheric pleural pressure causes atelectasis, which can be further aggravated by manipulation and retraction of the lungs during the surgical procedure. Atelectasis results in hypoxemia because there are regions of ventilation-perfusion mismatch and shunt. Hypoxemia due to atelectasis and shunt will not respond well to oxygen supplementation. Use of positive end-expiratory pressure at the end of the surgery and before the thoracic cavity is closed will help correct the atelectasis and may help relieve postoperative hypoxemia.[4]

148.3.2 Reduction of Venous Return

With the loss of subatmospheric intrapleural pressure, the large intrathoracic veins have a tendency to collapse, which can cause a reduction in venous return and cardiac output. Residual pneumothorax and fluid accumulation during the postoperative period can also contribute to hemodynamic compromise. These effects are aggravated by fluid losses during surgery. Volume loading the patient before surgery with crystalloid or colloid fluids to a central venous pressure of 6 to 7 cm H_2O will help prevent the reduction in cardiac output. Volume loading has to be performed with caution in the patient with cardiac disease, and monitoring of central venous pressure is advised to guide this therapy.

148.3.3 Hypothermia

Opening of the thoracic cavity with a median sternotomy or an intercostal approach results in a significant drop in the patient's body temperature because of the increase in the surface area exposed to room air. The longer the surgery, the more pronounced the reduction in temperature will be. This effect is even more significant in younger and smaller animals. Hypothermia causes severe cardiovascular, respiratory, electrolyte, acid-base, and coagulation abnormalities. Continuous temperature monitoring and active rewarming techniques are required during both the intraoperative and postoperative periods.

148.4 POSTOPERATIVE CONSEQUENCES OF THORACOTOMY

After thoracotomy, hypoxemia, residual pneumothorax, pleural effusion, and pain need to be corrected to help the patient restore normal pulmonary[5] and cardiovascular physiology.

148.4.1 Hypoxemia

Hypoxemia is a common problem after thoracic surgery. Hypoxemia during the recovery period is primarily a consequence of atelectasis that develops during the procedure. It can be aggravated during the postoperative period by lateral recumbency of the patient and pleural space disease. In lateral recumbency, the dependent lung is collapsed under the weight of the heart and any fluid accumulation. Ventilation is distributed mostly to the nondependent lung, and gravity distributes blood flow to the dependent lung that is not well ventilated. Therefore the ventilation-perfusion mismatch is worsened. It is very important to turn these patients regularly to reduce the ventilation-perfusion mismatch.[6]

148.4.2 Pleural Space Disease

Residual pneumothorax and accumulation of pleural effusion contribute to hypoxemia because they interfere 642
with lung reexpansion. Thoracostomy tube placement is paramount, and chest tube management is an important 643
aspect of postoperative care. Pneumothorax may be a result of incomplete evacuation of the pleural space at the end of the surgical procedure, or it can be secondary to a pulmonary lesion as a result of the surgery or the primary disease process. Mild to moderate pleural effusion is not uncommon following thoracotomy. Fluid is frequently hemorrhagic in nature, and the volume of fluid production will vary with the nature of the procedure. Large volumes of frank blood (confirmed by a fluid packed cell volume equal to or greater than the peripheral packed cell volume) is of concern, and a surgical consultation should be sought.

148.4.3 Pain

Thoracotomy is a painful procedure because of the retraction of the rib cage. Pain will prevent full excursion of the thoracic wall, which will impair ventilation and further encourage atelectasis. Therefore pain can contribute to hypoxemia. Pain is also associated with catecholamine release, contributing to vasoconstriction, reduction of tissue perfusion, tachycardia, and arrhythmias. Pain management helps reduce the incidence of tachycardia and arrhythmias during the postoperative period. Consequently, pain management is an essential component of the postoperative care of these patients.

However, pain medications, especially opioids, can have a significant depressant effect on the respiratory center. Therefore a good balance between pain control and effective respiratory function is required. Short-acting opioids like fentanyl are recommended, because their effect can be adjusted quickly to patient needs.[3,7] Intercostal nerve blocks at the end of an intercostal thoracotomy are highly recommended. Injection of lidocaine and bupivacaine in the interpleural space is another very efficient technique to control postoperative pain without affecting ventilation.[7,8] Epidural analgesia has also been reported as an efficient technique to control pain without interfering with ventilation[9,10] (see Chapter 164, Analgesia and Constant Rate Infusions).

148.5 POSTTHORACOTOMY MONITORING

During the postoperative period it is important to monitor cardiac and pulmonary function.[6,11,12] The goal of postoperative care is to optimize oxygen delivery, which is a function of cardiac output and arterial oxygen content. Heart rate, arterial blood pressure, central venous pressure, and urine production are monitored constantly for the first 24 hours after surgery. Arterial blood gas analyses are performed to follow the progression of ventilation and hypoxemia, and to guide oxygen supplementation. Hematocrit and total protein concentrations are optimized to allow better oxygen delivery.

148.5.1 Cardiovascular Function

148.5.1.1 Arrhythmias

Ventricular arrhythmias are very common after thoracic surgery, especially cardiac surgery. Hypoxemia, pain, manipulation of the heart, and surgical trauma to the myocardium contribute to arrhythmias. Consequently, continuous electrocardiographic monitoring of these patients during the postoperative period is recommended. General criteria have been established for management of ventricular arrhythmias. Usually, sustained ventricular tachycardia with a rate above 160 beats/min, multiform ventricular premature contractions, and the R on T phenomenon are all considered indications for medical management in an effort to prevent deterioration into ventricular fibrillation. The most common antiarrhythmic drug used to correct ventricular arrhythmias is lidocaine. A bolus of 1 to 2 mg/kg is given to test the response of the patient and is followed by a constant rate infusion of 25 to 100 µg/kg/min. Hypokalemia can impair the effectiveness of lidocaine and should be treated aggressively with potassium supplementation. Magnesium chloride can also be used to manage ventricular arrhythmias in dogs at the dosage of 0.75 mEq/kg/IV q24h intravenously (see Chapter 47, Ventricular Tachyarrhythmias). Pain medication and oxygen therapy are optimized to augment arrhythmia management, because catecholamine release and endocardial ischemia contribute to ventricular tachycardia.

148.5.1.2 Hypotension

Hypotension is a common complication after thoracotomy, and blood pressure monitoring is essential. Continuous direct arterial blood pressure monitoring via an indwelling arterial catheter is ideal, but indirect oscillometric or Dop-pler monitoring is acceptable. The most common cause of hypotension is hypovolemia. Hypotension can result from reduced cardiac function or severe vasodilation due to severe systemic inflammatory response syndrome and sepsis. Crystalloid fluid therapy with or without synthetic colloid administration is an essential aspect of postoperative care (see Chapter 65, Shock Fluids and Fluid Challenge). In addition, blood products should be administered as required to maintain hematocrit and coagulation parameters in the optimal ranges. Central venous pressure monitoring can help optimize fluid therapy and is recommended in cases of persistent hypotension. Central venous pressure should be maintained between 3 and 5 cm H_2O in the patient without cardiac disease. If the patient has cardiac disease such as mitral valve regurgitation or cardiomyopathy, it is important to prevent volume overload.

148.5.1.3 Lactate

Elevated blood lactate levels in the postoperative patient are a reliable indicator of poor tissue oxygen delivery. Measurement of blood lactate concentration should be performed regularly (every 2 to 4 hours) during the immediate postoperative period. The normal lactate level is less than 2 mmol/L. Increased levels should prompt an evaluation of perfusion and oxygenation indexes and appropriate therapy instituted.

148.5.2 Respiratory Function

148.5.2.1 Hypoxemia

Hypoxemia after thoracic surgery is commonly due to hypoventilation and atelectasis, although underlying pulmonary pathology and aspiration pneumonia can also be present. Residual gas anesthetic, residual pneumothorax, pleural effusion, and pain are factors that commonly affect respiratory function. For this reason monitoring of oxygenating ability during the recovery period is essential, and oxygen administration should be provided as indicated. Intermittent arterial blood gas analysis is recommended. Continuous or intermittent pulse oximetry can be used in conjunction with arterial blood gas analysis to detect acute deteriorations in patient oxygenating ability. In the absence of arterial blood gas measurement, pulse oximetry must be relied on, but the limitations of this monitoring device should be recognized.

Hypoxemia is defined as a partial pressure of oxygen in the arterial blood (PaO_2) of less than 80 mm Hg, which is equivalent to a saturation of 95%. A PaO_2 less than 60 mm Hg is considered severe hypoxemia (oxygen saturation of 90%). It is important to maintain the PaO_2 above 60 mm Hg because below this level hemoglobin saturation decreases precipitously, leading to significant compromise of oxygen delivery. Supplemental oxygen should be administered as needed to maintain the saturation above 95% (above 90% as an absolute minimum). Oxygen can be delivered by a mask, a nasal cannula, or by placing the patient in an oxygen cage. If the PaO_2 cannot be kept above 60 mm Hg despite therapy, mechanical ventilation is indicated. Thoracic radiographs to definitively rule out pleural space disease should be considered before initiating mechanical ventilation.

148.5.2.2 Ventilation

Ventilation is best evaluated by the partial pressure of carbon dioxide in arterial or venous blood. If the partial pressure of carbon dioxide is higher than 45 mm Hg, alveolar ventilation is inadequate. If hypoventilation develops, the thoracostomy drain should be checked to eliminate residual pneumothorax or fluid accumulation in the pleural space. Analgesia is indicated in an attempt to allow a better excursion of the thoracic wall without compromising ventilation via depression of the respiratory centers. If hypoventilation is thought to be due to excessive narcotic drug administration, reversal with naloxone or partial reversal with butorphanol should be considered. If significant hypoventilation persists (partial pressure of carbon dioxide >60 mm Hg) despite medical therapy, mechanical ventilation is indicated.

148.5.2.3 Thoracostomy Tube

Thoracostomy tube management is a vital aspect of care for the postthoracotomy patient. The tube entry site should be clean and kept covered with a sterile dressing. The chest tube should be secured in two places to lessen the chance of inadvertently dislodging it, and it should be sealed securely with both three-way stopcock and a tube clamp (see Chapter 32, Thoracostomy Tube Placement and Drainage).

It is generally recommended to aspirate the chest tube every hour for the first 4 hours postoperatively and then every 4 hours thereafter. In some cases of severe pleural space disease, continuous suction via a 3-chamber apparatus may be indicated.

It is important to turn the patient regularly (every 2 to 4 hours) to reduce the development of atelectasis and to improve fluid drainage from the pleural space. If a patient develops hypoxemia, the chest tube should be aspirated immediately. If tube aspiration is unproductive, dislodgement of the chest tube and progressive pleural space disease should be ruled out as a possible cause of the hypoxemia. If tube aspiration is productive, the patient should be observed for an improvement in respiratory rate and effort and arterial blood gases measured to ensure the hypoxemia is corrected.

148.5.2.4 Temperature

Because these patients are prone to hypothermia, continuous or regular intermittent temperature monitoring is required. During the immediate postoperative period, active warming should be instituted until the patient's temperature reaches 99.5° F. Use of blankets and active warming should be guided by the animal's temperature for the rest of the recovery period.

148.6 SUGGESTED FURTHER READING*

A Tucker: Respiratory pathophysiology. In D Slatter (Ed.): *Textbook of small animal surgery*. 2003, Saunders, Philadelphia, *Excellent review of pulmonary physiology applied to the surgical patient.*

AE Wagner, JS Gaynor, CI Dunlop, et al.: Monitoring adequacy of ventilation by capnometry during thoracotomy in dogs. *J Am Vet Med Assoc*. **212**, 1998, 377, *Excellent manuscript to describe modification of pulmonary physiology during thoracotomy; illustrates an augmentation of dead-space ventilation*.

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* See the CD-ROM for a complete list of references

149 Chapter 149 Post–cardiac Surgery Management

E. Christopher Orton, DVM, PhD, DACVS

149.1 KEY POINTS

- Impaired cardiac function in the form of inadequate cardiac output or elevated end-diastolic pressure, or both, is often present in patients that have undergone cardiac surgery.
- Overzealous administration of crystalloid fluids should be avoided in animals undergoing cardiac surgery.
- Inadequate cardiac output after cardiac surgery is suggested by resting blood lactate levels greater than 2.5 mmol/L or oxygen extraction ratio over 40%.
- Cardiac function in animals undergoing cardiac surgery should be supported with inotropic and vasoactive drugs.
- Ventricular tachycardia and atrial fibrillation are the most important arrhythmias occurring in animals after cardiac surgery.

149.2 INTRODUCTION

Cardiac function is impaired when cardiac output is inadequate despite adequate ventricular end-diastolic pressure or when adequate cardiac output is maintained at the expense of elevated ventricular end-diastolic pressure. Generally animals undergoing cardiac surgery have varying degrees of impaired cardiac function before surgery.[1] Superimposed on this preexisting cardiac insufficiency are the detrimental effects that general anesthesia and thoracic surgery have on cardiopulmonary function. A positive element is that the cardiac repair should improve cardiac function. A guiding principle of cardiac surgery is that it should not be undertaken unless the prospect for improved cardiac function is significant.[2] Nevertheless, these patients do require some special considerations for supportive care during the period immediately after surgery.

149.3 FLUID THERAPY

Fluid therapy after cardiac surgery often presents a dilemma. On the one hand, most animals benefit from some degree of volume loading during and after surgery to counteract the negative effects of anesthesia and surgery on cardiovascular function. This would include animals with preexisting cardiac insufficiency. On the other hand, patients often enter cardiac surgery with varying degrees of heart failure, and like any animal with heart failure, will not tolerate large loads of crystalloid fluids. The goal of fluid therapy in these patients is to maintain a vascular volume adequate to support cardiac function without worsening or precipitating congestive heart failure.

Assessments of vascular volume include body weight, central venous pressure (CVP), and pulmonary wedge pressure. The latter is ideal for animals with left-sided cardiac insufficiency but is not generally available. Thus body weight, CVP, and good clinical judgment are the best guides to fluid therapy. Preoperative body weight and CVP serve as good guidelines for the postoperative period if the animal was stable entering surgery. In general, a CVP of 4 to 8 cm H_2O (3 to 7 mm Hg) is a reasonable therapeutic target. It is important to realize that animals with cardiac insufficiency are more likely to be volume overloaded than hypovolemic after cardiac surgery.

Overzealous fluid therapy is detrimental and inappropriate. As a general rule, animals should not receive higher than maintenance rates of crystalloid fluids after cardiac surgery. In fact, animals may be trying to excrete excess body water and sodium if the cardiac repair has substantially improved cardiac function. These animals may benefit from having little or no crystalloid fluid therapy. If blood volume is inadequate or there is ongoing loss of volume due to surgical bleeding, then volume replacement should take the form of colloid-type fluids such as fresh whole blood, plasma, washed red blood cells, or albumin. The hematocrit, plasma total solids, total protein, and colloid osmotic pressure serve as guides for the type of colloid fluid administered. Animals should be monitored closely for evidence of pulmonary or systemic congestion after cardiac surgery. If congestion develops, intravenous furosemide (2 mg/kg bolus or 0.25 mg/kg/hr constant rate infusion [CRI]) is indicated.

149.4 CARDIAC OUTPUT

Animals should be monitored for adequacy of cardiac output after cardiac surgery. Inadequate cardiac output is suggested by a resting blood lactate concentration greater than 2.5 mmol/L, mixed venous oxygen saturation less than 70%, or oxygen extraction ratio of over 40%.[3] Low mean systemic arterial pressure suggests the possibility of, but does not confirm, inadequate cardiac output. Moderate hypotension (mean arterial pressure of 60 to 75 mm Hg) with evidence of generalized vasodilation (i.e., pink mucous membranes) and without evidence of inadequate cardiac output is well tolerated and does not generally require therapy to augment cardiac output. On the other hand, hypotension in a patient with generalized vasoconstriction (i.e., white mucous membranes, cold extremities) suggests that cardiac output may be inadequate.

Animals with evidence of inadequate cardiac output with or without concurrent hypotension should receive supportive therapy to improve cardiac output. Hypovolemia should be corrected, if present, but aggressive volume loading is not appropriate for animals with cardiac insufficiency. Therapeutic support of cardiac output takes the form of drugs or drug combinations with inotropic and vasomotor effects.

The choice of drugs is influenced by several factors, including the magnitude and chronicity of myocardial failure, mean arterial pressure, and renal function (Table 149-1).[4]

- *Dobutamine*, a synthetic analog with predominant β-agonist activity, is administered when inotropic support of the myocardium is desired. Stimulation of peripheral β_2-receptors promotes vasodilation and can contribute to hypotension on occasion.
- *Milrinone*, a phosphodiesterase 3 inhibitor, is a potent positive inotrope with moderate vasodilation activity. It is used alone or in combination with β-agonists to achieve an inotropic effect, especially when myocardial β-receptor down-regulation is suspected (i.e., chronic myocardial failure).
- *Epinephrine*, a β-agonist and α-agonist, is used when both inotropic and vasopressor effects are needed to support cardiac output and correct severe hypotension. Its principal indication is during and immediately after cardiac surgery.
- *Dopamine* is a dopaminergic β-agonist and α-agonist, with effects that depend on the dosage. At lower dosages, dopamine supports myocardial function through its beta effect and improves blood flow to the kidneys, heart, brain, and mesenteric organs through dopaminergic receptors. At higher dosages, dopamine adds an α-mediated vasopressor effect.
- *Phenylephrine*, an α-agonist, can be administered alone or in combination with other drugs when a pure vasopressor effect is necessary.

All of the above drugs carry a significant risk of promoting tachycardia and arrhythmias. Animals should be monitored for these adverse effects. Benefits and hazards of inotropic support should be weighed carefully in each patient.

149.5 ARRHYTHMIA MANAGEMENT

Arrhythmias are common after cardiac surgery, especially in an animal with preexisting myocardial dysfunction. Arrhythmias can cause considerable morbidity after cardiac surgery and increase the risk for sudden cardiac arrest. Arrhythmias encountered after cardiac surgery include both tachyarrhythmias and bradyarrhythmias. Tachyarrhythmias include sinus tachycardia, ventricular ectopy including ventricular tachycardia, atrial fibrillation or flutter, and the supraventricular tachycardias. Bradyarrhythmias include sinus bradycardia, atrial standstill, and atrioventricular block.

Sinus tachycardia is often present after cardiac surgery. Management should be directed toward relieving its underlying causes including pain, apprehension, cardiovascular instability, or drug therapy (e.g., inotropic drugs).

Table 149–1 Drugs Used to Support Cardiovascular Function After Cardiac Surgery

Drug	Action	Dosage	Indication	Side Effects
Epinephrine	β-Agonist, α-agonist	0.05 to 0.5 μg/kg/min IV CRI	Inotropic support and vasopressor	Tachycardia, arrhythmias
Dobutamine	β_1-Agonist, β_2-agonist	1 to 20 μg/kg/min IV CRI	Inotropic support	Tachycardia, arrhythmias
Milrinone	PDE-3 inhibitor	0.1 to 0.5 μg/kg/min IV CRI	Inotropic support and vasodilation	Tachycardia, arrhythmias, hypotension
Dopamine	Dopaminergic β-agonist α-Agonist at higher dosages	1 to 10 μg/kg/min IV CRI	Inotropic support and renal vasodilation Vasopressor effect at high dosages	Tachycardia, arrhythmias
Phenylephrine	α-Agonist	1–4 μg/kg/min IV CRI	Vasopressor	Decreases cardiac output

CRI, Constant rate infusion; *IV,* intravenous; *PDE,* phosphodiesterase.

Ventricular ectopy in the form of ventricular premature contractions, ventricular couplets and triplets, or paroxysmal or sustained ventricular tachycardia are encountered frequently after cardiac surgery. Not all ventricular ectopy requires treatment. Ventricular premature contractions are not generally dangerous or associated with hemodynamic alterations, and they do not generally require therapy. Sustained ventricular tachycardia, paroxysmal ventricular tachycardia that is unstable (i.e., close or irregular QRS coupling), or multifocal ventricular ectopy should be suppressed. Lidocaine (2 mg/kg IV boluses, then 50 to 80 μg/kg/min CRI) is usually the initial therapy of choice for ventricular ectopy. Fast sustained ventricular tachycardia that causes hemodynamic instability and is not responsive to IV lidocaine should be terminated with synchronous direct current cardioversion. Slower sustained ventricular rhythms (<120 beats/min) in which the suspected cause is a protected automatic focus (ventricular parasystole) are generally not harmful, are difficult to suppress, and do not require intervention.

Chronic atrial fibrillation that is present before surgery will likely require rate-control therapy during the perioperative period. Diltiazem (2 to 6 μg/kg/min IV CRI) is usually the most reliable therapy until oral administration can be reinstituted. The therapeutic goal is to reduce the ventricular rate to less than 150 beats/min. Acute atrial fibrillation and flutter are common arrhythmias after cardiac surgery, especially in dogs undergoing valve repair or replacement. Animals that develop atrial fibrillation or flutter after cardiac surgery that are otherwise stable should undergo rate-control therapy with IV diltiazem. Animals that are hemodynamically unstable as a result of the atrial fibrillation or flutter should undergo electrical cardioversion. If the arrhythmia was not present before surgery, then it may revert spontaneously to normal sinus rhythm after cardiac surgery. Animals that do not spontaneous revert to sinus rhythm by 6 weeks after surgery should undergo elective cardioversion by administration of amiodarone (10 to 15 mg/kg PO q24h for 1 week, then 5 to 7.5 mg/kg PO q24h thereafter) followed by synchronous direct current cardioversion, under anesthesia if necessary. Oral β-antagonist (continuous release metoprolol [Toprol XL] 0.4 to 1 mg/kg q24h) therapy administered before and as soon as feasible after elective cardiac surgery may decrease the incidence of atrial fibrillation or flutter in dogs undergoing valve surgery.[5] Administration of oral amiodarone 6 days before and 6 days after cardiac surgery has also been shown to reduce the incidence of atrial tachyarrhythmias after cardiac surgery in human patients.[6] The latter effect is enhanced by concurrent β-antagonist therapy.

Sinus bradycardia in animals with adequate cardiac output does not require management. Atrial standstill (i.e., bradycardia with loss of P waves) is most likely the result of hyperkalemia. Emergency treatment is directed toward lowering the serum potassium concentration and correcting the underlying cause. Complete atrioventricular block with ventricular escape may result from injury to the cardiac conduction system during cardiac repair. The only effective treatment is temporary ventricular pacing followed by implantation of a permanent pacemaker if the block does not resolve within a few days of surgery.

149.6 OTHER SUPPORTIVE CARE

Other supportive care for animals undergoing cardiac surgery include support of pulmonary function, management of the pleural space, intervention for postoperative bleeding, maintenance of renal and gastrointestinal function, wound management, and postoperative pain management (see Chapters 148 and 150, Postthoracotomy Management and Management After Cardiopulmonary Bypass, respectively).

149.7 SUGGESTED FURTHER READING*

ed 2, PR Fox, Sisson, D, Moïse, NS (Eds.): In *Textbook of canine and feline cardiology*. 1999, Saunders, Philadelphia, *Comprehensive review of the causes and management of heart disease in small animals, including causes and management of heart failure, and diagnosis and management of cardiac arrhythmias, with an appendix that includes dosages, indications, and side effects of cardiovascular drugs in dogs and cats*.

LH Opie: In *Drugs for the heart*. ed 5, 2005, Saunders, Philadelphia, *Excellent comprehensive but concise review of drug mechanisms, indications, side effects, precautions, contraindications of cardiovascular drugs in human patients; information that is very applicable to veterinary patients*.

EC Orton: Cardiac surgery. In DH Slatter (Ed.): *Textbook of small animal surgery*. ed 3, 2003, Saunders, Philadelphia, *Review of indications, technique, expected outcomes, and complications of cardiac surgeries performed in dogs and cats*.

* See the CD-ROM with a complete list of references

150 Chapter 150 Management After Cardiopulmonary Bypass

E. Christopher Orton, DVM, PhD, DACVS

Tracy L. Lehman, DVM, ACVECC board eligible

150.1 KEY POINTS

- Cardiopulmonary bypass (CPB) causes a systemic response characterized by generalized nonseptic inflammation, consumptive coagulopathy, and increased vascular permeability. Collectively this pathophysiologic response is termed the *systemic inflammatory response after bypass (SIRAB)*.
- Fluid support after CPB is directed toward maintaining adequate blood volume to support cardiac function while avoiding congestion of the lungs and other organs. Because of the effects of SIRAB on vascular permeability, over-administration of crystalloid fluids after CPB should be avoided.
- Coagulopathy and biologic bleeding are common during the first 12 hours after CPB. Management consists of administration of fresh frozen plasma, blood transfusion, and autotransfusion of washed shed red blood cells.
- Support of cardiopulmonary function after open heart surgery and CPB consists of administration of inotropic drugs, management of atrial and ventricular arrhythmias, and ventilator support.
- Support of renal function, gastrointestinal protection, and nutritional support are key elements after CPB in dogs.

150.2 INTRODUCTION

Cardiopulmonary bypass (CPB) is a procedure in which venous blood is diverted away from the heart and lungs to an extracorporeal system that oxygenates and pumps blood back to the arterial side of the systemic circulation. CPB provides a motionless and bloodless operative field and time to perform precise cardiac repair. CPB has been used to treat a variety of cardiac conditions in dogs.[1-10] The feasibility of CPB in cats has been demonstrated experimentally, although its use in the clinical setting has not yet been pioneered.[11] Dogs undergoing open heart correction under CPB require all of the considerations for care after cardiac surgery outlined in Chapter 149, Postcardiac Surgery Management, as well as a full understanding of the pathophysiologic consequences and special considerations for supportive care imposed by CPB itself.

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150.3 SYSTEMIC RESPONSE TO CARDIOPULMONARY BYPASS

CPB and open heart surgery expose the entire blood mass to biomaterials within the perfusion circuit and to nonendothelial surfaces within the wound. Further, CPB imposes the additional aberrations associated with significant dilution of the blood and whole-body hypothermia. Together these events initiate a systemic response mediated by contact activation of five blood cell types (neutrophils, platelets, endothelial cells, monocytes, lymphocytes) and five blood protein systems (intrinsic coagulation, extrinsic coagulation, fibrinolysis, kinin, and complement cascades).[12,13] These effects cause a pathophysiologic state of generalized nonseptic inflammation, consumptive coagulopathy, and increased vascular permeability collectively referred to as the systemic inflammatory response after bypass *(SIRAB)*. The SIRAB response has pathologic similarities to the systemic inflammatory response syndrome (SIRS) associated with sepsis and other generalized inflammatory states. It is critically important that the role that SIRAB plays in post-CPB patients be understood and considered when providing supportive care after open heart surgery.

150.4 FLUID AND ELECTROLYTE THERAPY

Supportive fluid therapy after CPB should be guided by the central venous pressure (CVP). The optimal CVP after CPB is generally between 4 and 8 cm H_2O (3 and 7 mm Hg). Insight about the optimal CVP for individual patients is gained during weaning from CPB. As with all cardiac surgery patients, the goal of fluid therapy is to maintain a vascular volume adequate to support cardiac function without worsening or precipitating congestion. An additional important consideration is the very considerable vascular permeability issue caused by CPB. In fact, the most common error in managing dogs after open heart surgery and CPB is the overadministration of crystalloid fluids resulting in significant third spacing of water and diminishing pulmonary and organ function. As a general rule, crystalloid fluids should not be administered at greater than maintenance rates and volumes. If additional fluid volume is necessary, it should take the form of colloid-type fluids such as fresh frozen plasma, 5% albumin, stored red blood cells (RBCs), whole blood, or washed autogenous RBCs (see following discussion of coagulopathy and hemorrhage). Choice of colloid-type fluid support is determined by availability and guided by the therapeutic goals of maintaining the total plasma protein over 4 g/dl, colloid osmotic pressure over 12 mm Hg, and packed cell volume over 30%. Synthetic colloid solutions (e.g., hydroxyethyl starch [hetastarch]) should be avoided after CPB because of their effect on coagulation and tendency to leak out of the vascular space.

Electrolyte abnormalities are often present after CPB. Several factors contribute to these abnormalities, including hemodilution from CPB priming solutions, infusion of cardioplegia solutions into the bypass circuit, and hormonal aberrations caused by surgery, CPB, and heart failure. Hypocalcemia is invariably present in dogs during and after CPB, especially in small dogs. Hypocalcemia is corrected by intravenous bolus administration of calcium chloride (10 mg/kg) during weaning and during the first 1 to 2 hours after CPB. Ionized calcium should be maintained above 1 mmol/L. Supplementation of calcium beyond the first few hours after CPB is generally not necessary. Administration of calcium salts to boost cardiac function in dogs that are not hypocalcemic should be avoided.

Hypokalemia is often present after CPB in dogs despite the infusion of high-potassium cardioplegia solutions during bypass. Because of its proarrhythmic effects, hypokalemia should be corrected within the first few hours after CPB by constant rate infusion (CRI) of potassium chloride (0.25 mEq/kg/hr) until the serum potassium level is greater than 3.5 mEq/L. After the initial correction of hypokalemia, addition of potassium chloride to maintenance fluids (20 to 30 mEq/L) is generally adequate to maintain potassium levels.

Both hyponatremia and hypernatremia can occur in dogs after CPB. Both of these abnormalities are most likely to develop during the first 24 hours after CPB and thus sodium levels should be monitored every few hours during this period. Hypernatremia is more likely to develop in dogs undergoing mitral valve surgery that had severe preoperative congestive heart failure (CHF). If hypernatremia develops (sodium level >155 mEq/L), then a low-sodium crystalloid fluid (e.g., 0.45% saline) should be administered. Judicious administration of furosemide (0.1 to 0.2 mg/kg IV q2-4h) may also be necessary to counter inappropriate sodium retention. It may take several days for hypernatremia to resolve once it develops. Lastly, hypomagnesemia commonly occurs after CPB. Prophylactic treatment of this deficiency with intravenous magnesium supplementation (0.75 mEq/kg/day) decreases the likelihood of post-CPB atrial and ventricular arrhythmias.

150.5 COAGULOPATHY AND HEMORRHAGE

CPB must be conducted under a state of complete anticoagulation. During CPB, activated clotting time (ACT) is maintained at over 480 seconds with administration of sodium heparin (300 U/kg IV). After termination of CPB, the effects of heparin are reversed with protamine sulfate (0.5 to 1 mg/kg IV) to return the ACT to preoperative levels. After protamine administration, a unit of fresh whole blood is given to replace cells lost during CPB, including platelets. Antifibrinolytic therapy during CPB is undertaken by administration of ε-aminocaproic acid (Amicar) by CRI (15 mg/kg/hr) to decrease intravascular fibrinolysis.

Despite these efforts to reduce the effects of CPB, coagulopathy is invariably present during the first 12 to 24 hours after CPB. Coagulopathy results from any of several causes, including dilution and consumption of coagulation factors, consumptive thrombocytopenia, platelet dysfunction, intravascular fibrinolysis, and incomplete reversal of heparin.[14] Coagulation status should be assessed periodically after CPB and should include ACT, prothrombin time, activated partial thromboplastin time, and platelet counts. Comparison of ACT with and without heparinase provides information about residual unbound heparin that could be contributing to coagulopathy.

Hemorrhage into the pleural space is a frequent complication after CPB in dogs. Hemorrhage after CPB can be surgical (i.e., inadequate closure of cardiotomy sites) or biologic (i.e., coagulopathy). Distinguishing between surgical and biologic bleeding can be very difficult after CBP. If surgical hemorrhage is suspected, then returning to the operating room is the most appropriate option. If hemorrhage is the result of biologic derangement, then supportive care and time is the best option. The volume of bleeding alone does not distinguish between surgical and biologic bleeding, because both can result in considerable hemorrhage. The best assurance that bleeding is biologic rather than surgical comes from confidence of the surgical team that cardiotomy incisions were closed well. If in doubt, biologic bleeding should be assumed and a conservative approach of time and supportive care adopted.

Time and supportive care are often the best treatment for coagulopathy after CBP. Supportive care consists of treating the underlying causes of coagulopathy, replacement therapy for lost RBCs. Administration of fresh frozen plasma to replace lost coagulation factors is helpful. Supportive care during hemorrhage consists of administration of type stored RBCs and autotransfusion of shed blood. Shed blood should be washed in a cell washer before it is readministered to the patient. Most dogs will require autotransfusion of washed shed blood after CPB. In general, biologic bleeding will diminish by 12 to 18 hours after surgery.

150.6 CARDIAC SUPPORTIVE CARE

Patients undergoing open heart surgery and CPB by their very nature have compromised cardiac function going into the procedure. Superimposed on that dysfunction are the insults imposed by cardiac surgery, cardioplegic cardiac arrest, and CPB.[15] The combined effect of these insults is myocardial injury that, in turn, compromises systolic function and predisposes to atrial and ventricular arrhythmias. Most, if not all, dogs undergoing CPB will require some degree of inotropic support and arrhythmia management after surgery (see Chapter 149, Post-Cardiac Surgery Management).

150.7 PULMONARY SUPPORTIVE CARE

The lung is a target organ for the adverse effects associated with SIRAB.[16] Pulmonary vascular injury and leak (“pump lung”) should be anticipated in all dogs undergoing CPB. Pulmonary dysfunction may not be apparent during the first hours after surgery but will become apparent by 4 to 6 hours after surgery. Preexisting pulmonary conditions such as chronic bronchitis and chronic left-sided CHF will add to the degree of pulmonary dysfunction after CPB, and these factors should be considered in case selection for cardiac surgery.

Arterial blood gases should be monitored every 2 to 4 hours during the first 24 hours after CPB. Pulmonary dysfunction manifests as varying degrees of hypoxemia caused by impaired gas exchange and hypoventilation. Impaired gas exchange results from a combination of ventilation-perfusion inequality and pulmonary shunt and, depending on the relative distribution of these mechanisms, responds to supplemental oxygen to varying degrees. Hypoventilation results from the combined effects of sedation associated with analgesia and residual anesthetic drugs and decreased pulmonary compliance.

Most dogs will require ventilator support for at least a few hours after CPB. The amount of time depends on the procedure, the size of the dog, the duration of CPB, and preexisting pulmonary disease. Dogs undergoing mitral surgery, small dogs, and dogs with chronic bronchitis are likely to require longer artificial ventilation. Most dogs can be weaned from a ventilator by 12 hours after CPB. Thereafter supplemental oxygen will generally be required for an additional 24 to 48 hours (see Chapters 213 and 214, Basic Mechanical Ventilation and Advanced Mechanical Ventilation, respectively).

150.8 RENAL SUPPORTIVE CARE

Renal function can be altered in patients that have undergone CPB, secondary to both predisposing patient factors and physiologic alterations that occur during the perioperative period. The mortality rate in human patients who develop renal failure after cardiac surgery is over 50%, despite appropriate and intensive therapy.[17] Fortunately, renal failure is a relatively rare occurrence after cardiac surgery, although mild renal impairment occurs more frequently. Dogs have been found to develop hematuria and renal tubule swelling post experimental CPB.[18] Even mild renal dysfunction results in increased morbidity and length of hospitalization for these patients.

The two most important risk factors for renal failure in patients after CPB are renal ischemia secondary to decreased cardiac output and preexisting diminished renal functional reserve.[19] Perioperative cardiac dysfunction, lengthy procedures, and a need for postoperative vasopressor drug support increase the risk of renal ischemia. Renal functional reserve tends to be decreased in older patients with more advanced disease. Renal protective strategies for patients undergoing CPB should focus on avoiding renal hypoperfusion by maximizing cardiac output and minimizing surgery time.

Renal function is evaluated by monitoring urine production, urine concentrating ability, electrolytes, and degree of azotemia. These parameters should be evaluated at least every 4 hours after CPB. The presence of azotemia or oliguria suggests insufficient cardiac output. Oliguria after CBP should be treated with intravenous furosemide and drugs to improve cardiac output and renal blood flow. Polyuria with an inability to concentrate urine can indicate medullary washout secondary to preoperative high-dose diuretic therapy, preexisting renal insufficiency, or CPB-related injury. CRI of dopamine to improve cardiac output and renal blood flow is an appropriate treatment for renal insufficiency in dogs after CPB. Appropriate fluid support is important, but most post-CPB patients will not tolerate high-volume administration of crystalloid fluids to support renal function.

150.9 GASTROINTESTINAL SUPPORTIVE CARE

High mortality rates are associated with gastrointestinal (GI) complications after CPB. As with renal dysfunction, GI, hepatic, and pancreatic complications are associated with multiple factors including prolonged duration of CPB, advanced age and concomitant disease, low cardiac output, and vasopressor therapy. Gastric mucosal pH is often decreased during CPB in both human and animal studies, suggesting decreased splanchnic perfusion. GI permeability increases significantly, and endotoxemia due to translocation from the gut has been documented after CPB.[20,21]

Unfortunately, current clinical indexes are unable reliably detect splanchnic perfusion abnormalities, GI function, or gastrointestinal injury in the perioperative setting. Clinical signs of GI dysfunction are subtle, which contributes to delays in diagnosis and treatment. Clinical signs of impaired GI function include anorexia, vomiting, hematochezia, hematemesis, melena, decreased or absent borborygmus, and failure to produce stool. Bleeding, usually duodenal or gastric, is the most common GI complication noted in patients after CPB. Gastroprotective strategies including maximizing cardiac output, precipitous discontinuation of drug therapy, administration of gastroprotective medications, and nutritional support should be instituted if altered GI function is suspected. High-risk patients should be treated prophylactically during the perioperative period.

150.10 NUTRITIONAL SUPPORT

Many patients with advanced cardiac disease have clinical signs of cardiac cachexia. CPB and the postoperative medical therapy associated with it impair GI function in many patients. Decreased nutrient intake depresses the immune system and impairs wound healing, while early nutritional support can prevent such undesirable complications. Early enteral nutrition increases cardiac index and splanchnic blood flow in post-CPB patients.[22]

Nutritional support can be provided to post-CPB patients by both the enteral and parenteral routes. Enteral nutrition by voluntary oral consumption should begin as soon as the patient is ready, generally on the second or third day after surgery. Additional support can be provided with judicious use of parenteral nutrition, the absorption of which is not affected by GI dysfunction. Parenteral nutrition may be required in dogs with preexisting cardiac cachexia or in dogs with GI dysfunction that delays oral feeding by more than 3 days after CPB.

150.11 SUGGESTED FURTHER READING*

P Klement, PJ del Nido, L Mickleborough, et al.: Technique and postoperative management for successful cardiopulmonary bypass and open-heart surgery in dogs. *J Am Vet Med Assoc*. **190**, 1987, 869, *Description of method for CPB and mitral valve replacement in normal dogs.*

EC Orton, TA Hackett, K Mama, JA Boon: Technique and outcome of mitral valve replacement in dogs. *J Am Vet Med Assoc*. **226**, 2005, 1508, *Surgical technique and outcome of dogs undergoing mitral valve replacement.*

EC Orton, GD Herndon, JA Boon, et al.: Intermediate-term outcome in dogs with subvalvular aortic stenosis: Influence of open surgical correction. *J Am Vet Med Assoc*. **216**, 2000, 364, *Intermediate-term outcome of dogs after open resection for subvalvular aortic stenosis.*

EC Orton, K Mama, P Hellyer, TB Hackett: Open surgical repair of tetralogy of Fallot in two dogs. *J Am Vet Med Assoc*. **219**, 2001, 1089, *Surgical technique and outcome of dogs undergoing correction of tetralogy of Fallot.*

* See the CD-ROM for a complete list of references.

151 Chapter 151 Kidney Transplantation

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151.1 KEY POINTS

- Kidney transplantation is a viable option for cats in both acute and chronic renal failure.
- Careful case selection of a potential recipient is critical to prevent both short-term and long-term complications.
- Cats with a history of recurrent urinary tract infections or those with significant cardiac disease are not typically good candidates for the procedure.
- Lifelong immunosuppression is necessary and consists of a combination of the calcineurin inhibitor, cyclosporine (CsA), and a glucocorticoid, such as prednisolone.
- Postoperative hypertension is managed with hydralazine (2.5 mg SC for a 4-kg cat) to prevent central nervous system complications (i.e., seizures).
- If acute rejection is suspected, treatment should be initiated immediately to prevent graft loss.
- Treatment of complications secondary to long-term immunosuppressive therapy including mycobacterial infections, toxoplasmosis, and neoplasia have been largely unsuccessful.

151.2 INTRODUCTION

Kidney transplantation is an accepted treatment option for cats in both acute and chronic renal failure. Since its introduction to the veterinary community in 1987 by Drs. Clare Gregory and Ira Gorley from the University of California, Davis, School of Veterinary Medicine, it is estimated that over 400 cases of feline renal transplantation have been performed at various centers around the country. Information from different centers suggests that survival times are continuing to improve; however these cases remain a challenge for the veterinary clinician. This chapter will discuss the most up-to-date information with regard to case selection, preoperative and postoperative care, anesthetic and surgical management, and handling of the most common long-term complications.

151.3 CASE SELECTION

Thorough screening for a potential feline renal transplant recipient is critical to decrease the incidence of morbidity and mortality that can occur following the procedure. Although the best time to intervene with surgery is still subjective, clinicians with experience treating these patients suggest that the best candidate for renal transplantation is one in early decompensated renal failure.[1,2] Indications of decompensation include worsening of azotemia and anemia, as well as continued weight loss while receiving medical therapy. Some clinicians have been successful in altering the physical deterioration of individual patients for up to 2 years with either a percutaneous endoscopic gastrostomy or esophagostomy feeding tube[2] (KG Mathews, personal communication, 1998).

151.3.1 Box 151-1 Preoperative Screening for a Potential Feline Renal Transplant Recipient

- Complete blood count
- Serum chemistry profile
- Blood type and crossmatch
- Thyroid hormone
- Urinalysis, urine culture, urine protein-to-creatinine ratio
- Abdominal radiography
- Abdominal ultrasonography
- Thoracic radiography
- Electrocardiography, echocardiography, blood pressure
- Feline leukemia virus, feline immunodeficiency virus
- Toxoplasmosis titer, IgG and IgM

IgG, Immunoglobulin G; *IgM,* immunoglobulin M.

Both physical and biochemical parameters need to be evaluated carefully to determine if a cat is a suitable candidate. Cats should be free of other disease conditions including significant heart disease, recurrent urinary tract infections, uncontrolled hyperthyroidism, and underlying neoplasia. Cats with a fractious temperament are also often declined as candidates. Not enough information exists to determine if cats with diabetes or inflammatory bowel disease should be declined as potential candidates. Preoperative examination involves various laboratory tests including a complete blood count, biochemical evaluation, blood type, thyroid function studies, evaluation of the urinary tract (urinalysis, urine culture, urine protein-to-creatinine ratio, abdominal radiographs, abdominal ultrasonography), evaluation for cardiovascular disease (thoracic radiography, electrocardiography, echocardiography, blood pressure), and screening for infectious disease including feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), *Toxoplasma* titer, and immunoglobulin (Ig) G and IgM[3,4] (Box 151-1). There is no age restriction for a potential transplant recipient. The feline recipient must also have compatible blood (via crossmatch) to a prospective kidney donor and to two or three blood donor cats.

151.3.2 Evaluation of the Urinary Tract

Evaluation of the urinary tract is essential, particularly to rule out any underlying infection or neoplastic disease. If abdominal ultrasonography of the kidneys leads to a suspicion of feline infectious peritonitis (FIP) or 651
neoplasia, 652 a fine-needle aspirate or biopsy is recommended. If a patient has recently been treated for a urinary tract infection or has had recurrent urinary tract infections, but at the time of arrival has negative urine culture results, then a cyclosporine (CsA) (Neoral, Novartis) challenge is recommended before transplantation to determine if the cat will “break” with an infection. To perform this challenge, CsA is administered for

approximately 2 weeks at the recommended dosage for transplantation immunosuppression. The urine is evaluated for infection after therapeutic CsA blood levels have been achieved and at the end of the 2-week period. It is important to note that a negative urine culture result following a challenge will not guarantee that a patient will remain infection free following surgery and during long-term immunosuppression.

Finally, if unilateral or bilateral hydronephrosis is identified in any patient during the screening process, a pyelocentesis and culture are recommended before transplantation. The author has identified five cats with obstructive calcium oxalate urolithiasis that have had a negative culture result from urine collected via cystocentesis and a positive culture result from urine collected by pyelocentesis (LR Aronson, unpublished data, 2005). Immunosuppression in a patient harboring an infection can not only potentiate the rejection process, but also lead to increased morbidity and mortality.

151.3.3 Cardiovascular Disease

At the time of presentation for transplantation, a systolic murmur may be auscultated on physical examination. These are often physiologic murmurs associated with the anemia of chronic renal failure and may not represent significant heart disease.[1] In a recent study from the University of California, Davis, evaluating cardiac abnormalities in 84 potential transplant recipients, 78% of patients had abnormalities including both papillary muscle and septal muscle hypertrophy. The authors suggested that these changes may be related to hypertension, chronic uremia, age, or early changes of hypertrophic cardiomyopathy.[5] Cats with diffuse hypertrophic cardiomyopathy or those with congestive heart failure are declined as candidates for renal transplantation at our facility. A decision is made on a case-by-case basis in those cats with less severe disease.

151.3.4 Infectious Disease

If a cat's test results are positive for FeLV or the animal has an active FIV infection, it is declined as a candidate for transplantation. Additionally, all potential donors and recipients undergo serologic testing (IgG and IgM) for toxoplasmosis. *Toxoplasma gondii* can cause significant morbidity and mortality in both human and veterinary immunocompromised patients. As a matter of policy at our facility, seropositive donors are not used and seropositive recipients are placed on lifelong prophylactic clindamycin (25 mg PO q12h), which is started when immunosuppression is initiated. If the cat does not tolerate the clindamycin, other antibiotics such as trimethoprim-sulfamethoxazole (Tribrissen) have been used.

151.4 DONOR SELECTION

Kidney donors are typically between 1 and 3 years of age and in excellent health. Standard evaluation includes a complete blood count, serum chemistry profile, urinalysis and culture, FeLV and FIV testing, and a toxoplasmosis titer (IgG and IgM). The feline kidney donor must also have a compatible blood crossmatch to the recipient and be of a similar size. Additionally, we perform computed tomographic angiography on all of the donors to evaluate the renal vasculature and the renal parenchyma for any abnormalities that may preclude successful transplantation.[6]

151.5 PREOPERATIVE MANAGEMENT

On admission to the transplant facility, intravenous fluid therapy is begun with a balanced electrolyte solution at 1.5 to 2 times the daily maintenance requirements. This rate may vary in cases of severe dehydration or in cats with underlying cardiac disease. At some centers, hemodialysis is performed before transplantation for cats that are anuric or those with severe azotemia (blood urea nitrogen >100 mg/dl, creatinine >8 mg/dl).[7] Additionally, if the cat is hypertensive, the calcium channel blocker amlodipine (Norvasc, 0.625 mg/cat PO q24h) may be indicated before surgery. Anemia is typically corrected at the time of surgery with crossmatch-compatible whole blood or packed red blood cell transfusions. The first unit that is administered is one that has been previously collected from the kidney donor. If the patient has evidence of decreased oxygen delivery from the anemia, blood products can be given at the time of admission to the transplant facility. If a delay in the transplant procedure is expected, erythropoietin (Epogen) can be administered and may greatly reduce the need for blood products at the time of surgery. Dosage is 100 IU/kg 3 times per week for the first 1 to 2 weeks and then tapered accordingly. Phosphate binders and gastrointestinal protectants are given if deemed necessary (see Chapter 181, Gastrointestinal Protectants). If the cat is anorectic, a nasogastric, esophagostomy, or percutaneous endoscopic gastrostomy tube may be placed for nutritional support before surgery (see Chapter 13, Enteral Nutrition).

151.5.1 Immunosuppression for the Feline Renal Transplant Recipient

The immunosuppressive protocol used at our facility consists of a combination of the calcineurin inhibitor, CsA, and the glucocorticoid, prednisolone. Because of the small dosage of CsA that cats often require for immunosuppression, the liquid microemulsified formulation, Neoral (100 mg/ml), is recommended so that the dosage can be titrated for the individual cat.

CsA administration is begun 72 to 96 hours before transplantation at a dosage of 1 to 4 mg/kg PO q12h depending on the cat's appetite. In the author's experience, cats that are anorexic or are eating a minimal amount have a much lower drug requirement to obtain appropriate drug levels before surgery. Additional agents that inhibit P-450 may alter drug concentrations and should be used with caution in these patients. A 12-hour whole blood trough concentration is obtained the day before surgery so that the dosage can be adjusted preoperatively if necessary. The drug level is measured using high-pressure liquid chromatography. The goal is to obtain a trough concentration of 300 to 500 ng/ml.[4] This level is maintained for approximately 1 to 3 months following surgery and is then tapered to approximately 200 to 250 ng/ml for maintenance therapy. Prednisolone is administered beginning the morning of surgery. At our facility, prednisolone is started at a dosage range of 0.5 to 1 mg/kg PO q12h for the first 3 months and then tapered to q24h. It is important to note that protocols for both CsA and prednisolone vary among transplantation facilities.

A second protocol used by some clinicians for feline immunosuppression combines the antifungal medication ketoconazole (10 mg/kg PO q24h) with CsA and prednisolone.[8,9] Ketoconazole can affect CsA metabolism by inhibiting both hepatic and intestinal cytochrome P-450 oxidase activity, resulting in increased blood CsA concentrations.[9] Once ketoconazole is added to the immunosuppressive protocol, CsA and prednisolone are administered once a day, and CsA dosage is adjusted into the therapeutic range by measuring whole blood trough levels daily. This protocol may reduce the cost of CsA and be more appealing for owners whose work schedule does not permit twice daily medication administration.

151.6 ANESTHESIA MANAGEMENT

At the time of anesthesia induction, both the donor cat and the recipient are given cephalexin (22 mg/kg IV q2h). An epidural is given to both cats (bupivacaine 0.1 mg/kg and morphine 0.15 mg/kg) for analgesia. In addition to a peripheral catheter, a double-lumen indwelling jugular catheter is placed, preferably using the recipient right jugular vein. The left side of the neck is preserved in cases that need an esophagostomy tube. Using this catheter, blood products can be given as needed, blood sampled regularly for evaluation of blood gases, electrolytes, packed cell volume, and total protein, and central venous pressure monitored if needed. Because the procedure can last up to 6 hours, hypothermia is of serious concern. A Bair Hugger or heating pads, or both, are used throughout the procedure and esophageal temperatures are monitored continuously. Systemic arterial blood pressure is monitored regularly throughout the procedure in both cats using a Doppler technique. Intraoperative hypertension is treated with hydralazine (2.5 mg SC for a 4-kg cat) and intraoperative hypotension corrected by decreasing the concentration of inhalant anesthetic or by administering fluid boluses, blood products, or dopamine (starting at 5 μg/kg/min).

151.7 SURGERY

Each transplant procedure involves a team of three surgeons. The donor cat is brought into the surgical suite approximately 30 to 45 minutes before the recipient. During this time, the donor kidney will be prepared for the nephrectomy. When the abdominal incision is made, the donor is given a dose of mannitol (0.25 g/kg IV over 15 minutes) to help prevent renal arterial spasms, improve renal blood flow, and protect against injury that can occur during the warm ischemia period. The renal artery and vein are cleared of as much fat and adventitia as possible, and the ureter is dissected free to the point where it joins the bladder. The left kidney is preferred because it has a longer vein. It is essential, however, to harvest a donor kidney with a single renal artery at the point where the artery joins the aorta. A minimal length of 0.5 cm of single renal artery is necessary for the arterial anastomosis.[1] The nephrectomy will be performed when the recipient is prepared to receive the kidney. Fifteen minutes before nephrectomy, an additional dose of mannitol (1 g/kg IV) is given to the donor cat.

Most of the recipient surgery is performed using a microscope. The renal artery is anastomosed end-to-side to the caudal aorta (proximal to the caudal mesenteric artery), and the renal vein is anastomosed end-to-side to the caudal vena cava.[10] Partial occlusion clamps are used to obstruct blood flow in both the aorta and the caudal vena cava, and holes are created in both to match the size of the renal artery and vein. Both aorta and vena cava, as well as the allograft, are flushed with a heparinized saline solution. The renal artery is anastomosed to the aorta using 8-0 nylon in a simple continuous pattern, and the renal vein is anastomosed to the vena cava using 7-0 silk in a simple continuous pattern.

Once the vascular anastomosis is complete, a ureteroneocystostomy is performed using an intravesicular mucosal apposition technique. A ventral midline cystotomy is performed and the end of the ureter brought directly into the bladder lumen through a hole created at the bladder apex. The bladder is everted, the distal end of the ureter is excised, periureteral fat is removed, and the end of the ureter is spatulated. The ureteral mucosa is sutured to the bladder mucosa using either 8-0 nylon or 8-0 Vicryl in a simple interrupted pattern. Following completion of the anastomosis, the bladder is inverted and closed routinely. Before closure, a biopsy of one of the native kidneys is performed and the allograft pexied to the abdominal wall using six interrupted sutures of 4-0 polypropylene. The recipient's native kidneys are usually left in place to act as a reserve in case graft function is delayed (Color Plate 151-1). Patients with polycystic kidney disease are an exception, because at least one of the native kidneys often needs to be removed to make room in the abdomen for the allograft.

151.8 POSTOPERATIVE MANAGEMENT AND PERIOPERATIVE COMPLICATIONS

Following surgery, the recipient is maintained on IV fluid therapy that should be adjusted to the cat's renal function, hydration status, and oral water intake. Blood transfusions are given only if necessary. Minimal stress and handling and hypothermia prevention are critical during the early postoperative period. While a catheter is in place, the cat is maintained on IV antibiotic therapy (cefazolin, 22 mg/kg IV q8h). Once all catheters are removed, the cat is then maintained on oral antibiotic therapy (ampicillin-clavulanate [Clavamox] 62.5 mg PO q12h) for another 3 to 4 weeks or until the feeding tube is removed and CsA levels regulated. If *Toxoplasma* titers are positive, clindamycin

(25 mg PO q12h) is administered in conjunction with the immunosuppression and continued for the lifetime of the cat. Postoperative pain has been controlled successfully at our facility using buprenorphine (0.005 to 0.02 mg/kg IV q4-6h), hydromorphone (0.05 to 0.2 mg/kg or SC q4-6 h), or a constant rate infusion of butorphanol (0.1 to 0.5 mg/kg/hr). Initially blood work is performed twice daily to evaluate acid-base status, packed cell volume, total protein, electrolyte, and blood glucose levels and then tapered accordingly depending on the stability of the cat. A renal panel is checked every 24 to 48 hours, and a blood CsA level is checked every 3 to 4 days and the dosage adjusted accordingly. Voided urine is weighed and recorded when possible. Abdominal palpation is not allowed during the postoperative period. With improvement in azotemia and appropriate pain control, most cats will start eating within 24 to 48 hours following the surgical procedure. If the cat remains anorexic, a feeding tube may be necessary.

Because of the association between postoperative hypertension and postoperative central nervous system disorders including seizure activity, indirect blood pressure is monitored every 1 to 2 hours during the first 24 to 48 hours to assess for hypertension.[11] If the systolic blood pressure is equal to or greater that 180 mm Hg, hydralazine (2.5 mg SC for a 4-kg cat) is administered. The hydralazine dose can be repeated if the systolic pressure has not decreased within 15 to 30 minutes. If the cat is refractory to hydralazine, acepromazine (0.005 to 0.01 mg/kg IV) has been used. It is important to note that the incidence of hypertension and central nervous system (CNS) disorders is not seen with equal frequency among transplant centers, and thus the cause of CNS disorders in cats following renal transplantation still remains a challenge for some clinicians.[8]

Complications can also arise if postoperative hypotension occurs. At our facility, systolic blood pressure is maintained at 100 mm Hg or greater. Sustained hypotension can lead to poor graft perfusion and needs to be managed aggressively to prevent acute tubular necrosis and delayed graft function.

If surgery is technically successful, azotemia typically resolves within the first 24 to 72 hours following surgery. If improvement does not occur during this time or if improvement in renal function is initially identified but then worsens, an ultrasonographic examination of the allograft is recommended. The allograft should be evaluated for adequate blood flow, as well as any signs of a ureteral obstruction including hydronephrosis or hydroureter. If subsequent ultrasonographic evaluations reveal worsening hydronephrosis, then a ureteral obstruction should be suspected. The cat is taken back to surgery so that the allograft can be evaluated. In some cases, the ureter may need to be reimplanted into the urinary bladder. If graft perfusion is adequate and no signs of obstruction are present, then delayed graft function should be considered.

Cats without complications are discharged from the hospital when graft function appears adequate and the animal is clinically stable. Cats with delayed graft function can also be discharged if otherwise clinically stable. Improvement in graft function often occurs within the first few weeks following surgery. Medical management of the renal failure can be continued in this subset of patients until graft function returns to normal. If the transplanted kidney fails to function, a biopsy should be performed on it before retransplantation.

151.9 LONG-TERM MANAGEMENT AND COMPLICATIONS

Patients should be evaluated by their veterinarians once a week for the first 4 to 6 weeks initially, and then visits can be extended to monthly intervals depending on the cat's stability. During each examination, the cat should be weighed and blood work performed including a renal panel, packed cell volume, total protein level, CsA level, and a urinalysis if a free-catch urine sample is available. A complete blood count and serum chemistry panel should be performed every 3 to 4 months and if the cat has been diagnosed with underlying cardiac disease, an echocardiogram should be performed every 6 to 12 months. If a feeding tube has been placed, it should be removed once oral intake of food and water is deemed appropriate.

Renal complications following transplantation include renal rejection, calcium oxalate nephrosis, hemolytic uremic syndrome, and retroperitoneal fibrosis. Acute rejection can occur at any time but is most common within the first 1 to 2 months following surgery. Cats that are experiencing a rejection episode may or may not have overt clinical signs that include polyuria and polydipsia, lethargy, depression, and anorexia. For this reason, weekly blood sampling is essential during the early postoperative period. Histopathologic as well as sonographic and scintigraphic examination of allograft rejection in cats has been described.[12,13]

Sonographic examination often reveals a significant increase in cross-sectional area of the allograft, a subjective increase in echogenicity, and a decrease in corticomedullary demarcation.[13] Although normal allograft enlargement is expected during the first week postoperatively, a gradual decline should then occur. Rejection should be suspected if the renal enlargement persists or progresses beyond this period. If possible, before starting the rejection protocol, urine sediment should be evaluated to rule out an underlying infection. Suspected acute rejection episodes are managed with intravenous administration of CsA (6.6 mg/kg q24h given over 4 to 6 hours) and prednisolone sodium succinate (Solu Delta Cortef, 10 mg/kg IV q12h). Each milliliter of the CsA is diluted with 20 to 100 ml of either 0.9% sodium chloride or 5% dextrose.[14] The infusion of CsA can be repeated.

Another cause for the azotemia should be considered if the creatinine concentration does not improve within 24 to 48 hours. Chronic rejection is characterized by gradual loss of organ function over months to years, often without evidence of a rejection episode. The cause of chronic rejection is unknown. Hemolytic uremic syndrome is a rare, but fatal, side effect of CsA therapy. Patients develop hemolytic anemia, thrombocytopenia with rapid deterioration of renal function secondary to glomerular and renal arteriolar platelet and fibrin thrombi.[15] In the author's experience, the mortality rate has been 100%.

Results of a study suggest that renal transplantation is a treatment option for cats whose underlying cause of renal failure is associated with calcium oxalate urolithiasis. No difference in long-term outcome was found between a group of stone formers and a control group of cats whose underlying cause of renal failure was not related to urolithiasis.[16] Additionally, of 19 stone formers, 5 cats formed calculi within the allograft between 4 and 22 months postoperatively. Although formation of calculi in the allograft did not significantly reduce survival, cautious interpretation of the data is necessary until more patients are evaluated.

Another cause of recurrence of azotemia within the first few months following surgery is retroperitoneal fibrosis.[17] Abdominal ultrasonography in these patients reveals hydronephrosis with or without hydroureter, and occasionally a capsule can be identified surrounding the allograft. Surgery has been successful in relieving the obstruction and restoring normal renal function. The exact cause is unclear.

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Finally, complications may occur secondary to long-term immunosuppressive therapy. These have included chronic urinary tract infections and pyelonephritis, fungal infections, mycobacterial infections, toxoplasmosis, diabetes, and neoplasia. Bacterial urinary tract infections in the transplant patient cause direct morbidity and mortality due to the infection itself, and may also activate the rejection process. Treatment often includes long-term antibiotic therapy based on cultures and sensitivity. Two cats developed fatal mycobacterial infections following long-term immunosuppressive therapy; one cat had systemic involvement and the other a septic arthritis (LR Aronson, personal communication, 2005). Five cats died following a reactivation of a latent toxoplasmosis infection post transplantation. Attempts to treat systemic mycobacterial and toxoplasma infections in feline renal transplant recipients have resulted in poor outcomes. The prevalence of malignant neoplasia in cats following renal transplantation has been reported from 9.5% to 14%, with lymphoma being the most common type reported.[19] Treatment with chemotherapy has also resulted in poor outcomes. Patients that have developed diabetes following long-term CsA and steroid therapy have responded successfully to decreasing the dosage of the steroids or the CsA, or both. Some patients require insulin therapy.

151.10 CONCLUSION

Renal transplantation offers a unique method of management of renal failure in cats. Approximately 90% to 95% of cats recover sufficiently and will go home following renal transplantation, and approximately 70% of the cases are alive and continuing to do well 1 year after transplant. Owners need to understand the risks involved with the procedure and that it demands a commitment for the life of the animal.

151.11 SUGGESTED FURTHER READING*

CA Adin, CR Gregory, AE Kyles, et al.: Diagnostic predictors and survival after renal transplantation in cats. *Vet Surg*. **30**, 2001, 515, *An article that provides information regarding preoperative diagnostic results that predict postoperative complications and survival in the feline renal transplant recipient.*

LR Aronson, AE Kyles, A Preston, et al.: Renal transplantation in cats diagnosed with calcium oxalate urolithiasis: 19 cases (1997-2004). *J Am Vet Med Assoc*. **228**, 2006, 743, *A paper that describes the outcome of 19 cats that had a renal transplant performed because of renal failure secondary to calcium oxalate urolithiasis*.

CR Gregory, L Bernsteen: Organ transplantation in clinical veterinary practice. In DH Slatter (Ed.): *Textbook of small animal surgery*. 2000, Saunders, Philadelphia, *A chapter that provides an excellent overview to renal transplantation in the dog and cat.*

M Katayama, JF McAnulty: Renal transplantation in cats: techniques, complications, and immunosuppression. *Compendium*. **24**, 2002, 874, *An article that contains information regarding surgical technique including hypothermic storage, short-term and long-term complications, and techniques for immunosuppression used at the University of Wisconsin, Madison*.

KG Mathews: In *Renal transplantation in the management of chronic renal failure. Consultation in feline internal medicine*. ed 4, 2001, Saunders, Philadelphia, *An excellent overview of renal transplantation in the cat.*

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* See the CD-ROM for a complete list of references.

20

Chapter 201 Daily Assessment of the Critically ill Patient

Linda Barton, DVM, DACVECC

201.1

Box 201-1 Kirby's Rule of 20[1]

- Fluid balance
- Oncotic pull
- Glucose
- Electrolyte and acid-base balance
- Oxygenation and ventilation
- Mentation
- Perfusion and blood pressure
- Heart rate, rhythm, and contractility
- Albumin levels
- Coagulation
- Red blood cell and hemoglobin concentration
- Renal function
- Immune status, antibiotic dosage and selection, WBC count
- GI motility and mucosal integrity
- Drug dosages and metabolism
- Nutrition
- Pain control
- Nursing care and patient mobilization
- Wound care and bandage change
- Tender loving care

GI, Gastrointestinal; *WBC,* white blood count.

201.2 KEY POINTS

- Optimal care of the critically ill patient is provided for when information collected by physical examination and clinical observation is integrated with the results of ancillary tests and technologically derived data.
- The ideal monitoring plan allows for early detection of metabolic or physiologic derangements yet minimizes the risks for iatrogenesis, unnecessary expense to the client, and inappropriate use of intensive care unit resources.
- Use of a checklist of parameters to be evaluated will enhance both efficacy and efficiency of the critically ill patient's daily assessment.

201.3 INTRODUCTION

Daily assessment of the critical patient begins with a thoughtful, history-guided physical examination. In the increasingly technical environment of the intensive care unit (ICU), the hands-on clinical assessment of a patient may be deemed less important than numbers recorded on a flow sheet. It is important that laboratory data and monitored parameters do not eclipse the value of the clinical evaluation of the patient. Optimal care is provided when information collected by physical examination and clinical observation is integrated with the results of ancillary tests and technologically derived data. The combination of subjective and objective information should be used to develop the daily diagnostic, therapeutic, and monitoring plan for the critically ill patient.

The type and frequency of monitoring should be based on the underlying disease process, the physiologic reserve of the patient, and the degree of clinical suspicion. Clinicians should guard against “routine” monitoring. The ideal monitoring plan allows for early detection of metabolic or physiologic derangements yet minimizes the risks for iatrogenesis, unnecessary expense to the client, and inappropriate use of ICU resources. Selection of monitoring aids should be based on reliability, expense, practicality, and the value of the information gained. Particularly when choosing invasive monitoring techniques, risk to the patient must be weighed against potential benefit. Utility of a monitoring device is maximized when clinicians are familiar with the principles of the device, how to operate it, the reliability of the measurement, the range of normal values, the indications, contraindications, and complications of the technique, and how to troubleshoot technical problems that may arise.

Although monitoring is a vital component of ICU care, it is important to remember that it is not the monitoring, alone, that is beneficial or protective, but rather the clinician's interpretation of the data and actions based on changes in monitored parameters that are important. It is impossible for the presence of a monitoring device to alter outcome. A monitored variable is useful only if a change in that variable is linked to an intervention or therapy that affects outcome. In addition to evaluating functions or parameters pertinent to the primary disease process, the daily assessment should include surveillance for new problems, because a common cause of ICU morbidity and mortality is progressive physiologic dysfunction in organ systems remote from the site of the primary disease process. Use of a checklist has been promoted to enhance both efficacy and efficiency when caring for critically ill patients.[1] Box 201-1 lists 20 parameters that should be included in the daily assessment of every ICU patient. This chapter will review these 20 parameters. Many, if not all, of these systems have been discussed in detail elsewhere in this text.

201.4 KIRBY's RULE OF 20

201.4.1 Fluid Balance

Fluid balance can be extremely challenging to assess in the critically ill patient. It requires assessment of both the intravascular and interstitial fluid compartments, based on physical examination findings. These findings are integrated with knowledge of the patient's total fluid intake and output and an understanding of the underlying disease processes.

Mucous membrane color, capillary refill time, heart rate, pulse quality, extremity temperature, central venous pressure, and systemic blood pressure can be used to evaluate vascular volume. Interstitial volume is best evaluated by mucous membrane moisture, skin turgor, packed cell volume and total solid parameters, and serial measurements of body weight. Many critically ill patients have altered capillary permeability or decreased albumin levels. These changes alter the distribution of fluid between the vascular and interstitial fluid compartments, favoring movement of fluid from the vascular to the interstitial space. In this patient population, adequate or even increased fluid in the interstitial space does not ensure normal vascular volume (see Chapters 64 and 65, Daily Intravenous Fluid Therapy and Shock Fluids and Fluid Challenge, respectively).

201.4.2 Oncotic Pull

Colloid osmotic pressure (COP), the osmotic pressure exerted by large molecules, serves to hold water within the vascular space. It is normally created by plasma proteins, namely albumin, that do not diffuse readily across the capillary membrane. Inadequate COP can contribute to vascular volume loss and peripheral edema. Normal COP is approximately 20 mmHg. Patients with COP values less than 15 mmHg are at risk for peripheral edema. The correlation between the refractive index of infused synthetic colloids and COP is not known. Therefore changes in refractive index cannot be used to monitor colloid administration. COP can be measured directly with a colloid osmometer; however, it is not commonly done because using the machine is labor intensive (see Chapter 64, Daily Intravenous Fluid Therapy).

201.4.3 Glucose

Hypoglycemia can occur rapidly and unexpectedly in critically ill patients, so blood glucose concentration should be monitored routinely. The frequency of measurement will depend on the severity of illness and the nature of the underlying disease. In critically ill patients, blood glucose should be monitored at least every 12 hours. The development of hypoglycemia in a critically ill adult patient should prompt the consideration of sepsis. In hypoglycemic patients, glucose can be supplemented in the balanced electrolyte solution or provided through nutritional support (see Chapter 69, Hypoglycemia). Studies of human ICU patients have demonstrated increased morbidity and mortality associated with hyperglycemia.[2,3] Similar studies have not been performed in veterinary patients; however, the aim should be to maintain blood glucose between 80 and 140 mg/dl.

201.4.4 Electrolyte and Acid-Base Balance

Abnormalities in serum electrolytes are common in critically ill patients and can have devastating clinical consequences if not identified and corrected. Serum sodium, chloride, potassium, and calcium should be monitored and maintained within the normal ranges. Monitoring frequency will depend on the severity of illness, the nature of the primary disease process, and the owner's financial commitment but may be needed as frequently as every 1 to 2 hours in patients with rapidly changing conditions. In addition, magnesium depletion has been identified as a common electrolyte abnormality in critically ill veterinary patients. Refer to the Electrolyte and Acid-Base Disturbances section of this text for a full discussion of these topics.

Measurement of acid-base status has become routine with the development of portable, affordable blood gas monitors. Venous samples are useful for evaluation of the metabolic acid-base status. Bicarbonate and base excess are used to evaluate metabolic status, and partial pressure of carbon dioxide (PCO_2) is used to evaluate the ventilatory status. Interpretation of acid-base abnormalities can be aided by measurement of lactate and electrolyte concentrations. Assessment of acid-base status should be performed at least daily in critically ill patients and may be required 4 to 6 times daily in some animals.

201.4.5 Oxygenation and Ventilation

Compromised pulmonary function is a common issue for the critically ill patient. Many trauma patients have pulmonary contusions; aspiration pneumonia is a common sequela in postoperative and recumbent patients; and lung failure is a well-recognized complication of sepsis and diseases associated with systemic inflammation. Respiratory rate, breathing pattern, and lung sounds should be monitored several times daily. In high-risk patients or those with worsening respiratory signs, a more objective assessment of arterial oxygenation can be made by measuring the partial pressure of oxygen in arterial blood (PaO_2) or the hemoglobin saturation with pulse oximetry (SpO_2). The partial pressure of oxygen in venous blood cannot be used as a measure of pulmonary oxygenating ability.

Pulse oximetry provides a noninvasive, painless measurement of arterial oxygenation, permitting frequent or even continuous measurement in the unstable patient. Because of the shape of the oxyhemoglobin dissociation curve, pulse oximetry is not a sensitive marker of changes in pulmonary gas exchange. When SpO_2 is over 90% the oxyhemoglobin curve is relatively flat; large changes in PaO_2 are associated with small changes in SpO_2. It is, however, a good indicator of arterial oxygenation and of developing hypoxemia. Arterial blood gases provide a more reliable and sensitive measure of lung oxygenating ability. If performed using a direct arterial puncture, they may be limited to 2 to 3 times daily. If an indwelling arterial catheter is present, more frequent arterial blood gas measurements are feasible.

Carbon dioxide is measured as an indication of ventilation and pulmonary function. Carbon dioxide can be evaluated on arterial or venous blood. Venous carbon dioxide is usually 3 to 6 mm Hg higher than the arterial value. The frequency of measurement of PCO_2 will depend on the nature of the disease processes. In cases at high risk for hypoventilation, such as animals with central nervous system disease or neuromuscular disorders, end-tidal carbon dioxide monitoring can provide a continuous, noninvasive measure of $PaCO_2$.

201.4.6 Mentation

Any sudden change in mentation should prompt the clinician to evaluate serum osmolality (especially in animals 853
receiving parenteral feeding), blood glucose, or any potential cause of increased intracranial pressure (see 854
Chapter 8, Deteriorating Mental Status).

201.4.7 Perfusion and Blood Pressure

Inadequate blood pressure and tissue perfusion is common in critically ill patients and should be corrected rapidly. Decreased preload can be caused by increased fluid losses such as gastrointestinal or third-space loss, in addition to fluid leakage secondary to increased vascular permeability. Vasodilation of peripheral vessels and maldistribution of blood flow will cause a relative hypovolemia.

Clinically the six parameters used to assess perfusion are mentation, mucous membrane color, capillary refill time, heart rate, pulse quality, and extremity temperature. Blood pressure can be measured indirectly by Doppler or oscillometric techniques or directly via an indwelling arterial catheter. Blood pressure should be measured at least daily in critically ill patients. Continuous blood pressure monitoring maybe indicated for hemodynamically unstable patients. Hypotension is defined as a mean arterial pressure less than 70 mm Hg, and 60 mm Hg is considered the minimum pressure required to maintain adequate perfusion to the brain and kidneys.

It is important to note that patients can have poor perfusion while maintaining an adequate blood pressure. Global markers of anaerobic metabolism (base deficit, lactate) and of increased oxygen extraction (low mixed venous oxygen saturation) are more sensitive indicators of perfusion than blood pressure or physical examination parameters. When these markers were evaluated in human patients treated for hypovolemic shock, more than 80% of the patients with normal heart rate, blood pressure, and urine output were considered hypoperfused based on evidence of ongoing anaerobic metabolism and tissue acidosis.[4] If fluid therapy alone fails to restore adequate blood pressure and perfusion, catecholamine therapy should be added.

Hypertension, defined as a mean arterial pressure greater than 145 mm Hg, may develop in critically ill patients, especially those with renal disease, hyperthyroidism, hyperadrenocorticism, and neoplastic conditions (see Chapter 42, Hypertensive Crises).

201.4.8 Heart Rate, Rhythm, and Contractility

Critically ill patients are at risk of arrhythmias secondary to hypovolemia and hypoxemia. Tachycardia can be an early warning sign of hemodynamic compromise, and bradycardia can cause inadequate cardiac output and may be a sign of impending cardiac arrest. Heart rate and rhythm should be monitored regularly by auscultation or via an electrocardiogram. Continuous electrocardiographic monitoring can be invaluable in severely ill patients.

Tachycardia secondary to hypovolemia must be differentiated from elevated heart rates secondary to other causes of sympathetic stimulation such as pain and anxiety. Arrhythmias are common in critically ill patients and should be treated only if they are adversely affecting perfusion or are electrically unstable. Decreased cardiac contractility can be due to inherent cardiac disease such as cardiomyopathy or can be acquired. Inflammatory mediators including myocardial depressant factor cause decreased contractility. Echocardiography can provide a measure of contractility and can be used to guide inotropic therapy. Echocardiography is indicated in patients suspected to have primary cardiac disease or in patients with hemodynamic compromise that is not responding readily to fluid therapy.

201.4.9 Albumin

Hypoproteinemia is a common finding in critically ill patients. Total solids should be monitored at least daily and serum albumin should be monitored every 24 to 48 hours. Hypoalbuminemic animals may require support with synthetic or natural colloids. Although albumin levels less than 2 mg/dl have been associated with increased mortality in human patients, albumin transfusions to increase serum levels have not resulted in increased survival.

201.4.10 Coagulation

Coagulation abnormalities can be encountered in critically ill patients as a result of the primary disease process (e.g., vitamin K antagonist intoxication, hepatic disease), a coexisting disease process (e.g., von Willebrand disease, previous administration of nonsteroidal antiinflammatory drugs), or one acquired during the critical illness such as dilutional coagulopathy or disseminated intravascular coagulation (DIC). Evaluation of coagulation should be performed in all patients with active hemorrhage, all preoperative patients, and at-risk critically ill patients. Patients receiving anticoagulant or thrombolytic therapy may also require frequent monitoring of coagulation status. The tests chosen will depend on the patient's history, primary disease process, and test availability (see Chapter 118, Bleeding Disorders).

DIC should be anticipated in every critically ill patient. Early in the DIC process, animals are hypercoagulable; coagulopathy leading to signs such as bleeding from venipuncture sites suggests a very late stage in the process. Routine coagulation profiles do not reflect hypercoagulability. Minimally, activated clotting time and platelet count should be evaluated daily to monitor at-risk patients for progression into the hypocoagulable phase of DIC. Additional information can be obtained from full coagulation profiles, including activated clotting time, prothrombin time, partial thromboplastin time, fibrinogen, fibrin degradation products, and antithrombin III levels.

201.4.11 Red Blood Cell and Hemoglobin Concentrations

The oxygen content of arterial blood is dependent on the amount of functional hemoglobin, the degree of saturation of the hemoglobin, and the amount of dissolved oxygen in the blood. The most significant portion of the oxygen content of arterial blood is oxygen bound to hemoglobin. Hemoglobin concentration should be monitored at least daily and optimized to ensure adequate oxygen delivery. The optimal hematocrit value for oxygen transport is from 27% to 33%, and traditionally it has been recommended to maintain the packed cell volume in this range. More recent studies support a lower transfusion trigger of 7 g/dl of hemoglobin.[5] Transfusions of whole blood, packed red blood cells, or hemoglobin-containing solutions should be given as needed. Following administration of oxyglobin, hemoglobin levels can no longer be extrapolated from packed cell volume and must be measured directly.

201.4.12 Renal Function and Urine Output

Urine output should be monitored carefully in critically ill patients. Decreased urine output can reflect inadequate renal perfusion, inappropriate antidiuretic hormone secretion, or acute renal failure. Patients who have experienced hypotension during anesthesia or secondary to their underlying disease process are at risk of acute renal failure. In addition, these patients are often receiving potentially nephrotoxic drugs. Normal urine output in a well-perfused, normally hydrated patient is 1 to 2 ml/kg/hr. In both oliguric and polyuric patients, measurement of fluid intake and output can be used to facilitate fluid therapy.

Intake and output measurement requires a urinary catheter and closed collection system. Although an indwelling urinary catheter is associated with risk of infection, this can be minimized if care is taken with the placement technique, and the benefit of having an accurate measurement of urine output often outweighs the risk in this patient population.[6] Once a closed collection system is in place, urine volume should be measured at least every

4 hours. In the absence of an indwelling urinary catheter, estimates of urine output can be made by weighing absorbent pads or diapers placed under recumbent patients. Creatinine or blood urea nitrogen levels, or both, should be monitored daily during a crisis period. Urine should be evaluated daily for evidence of renal tubular casts or glucosuria.

201.4.13 Immune Status, Antibiotic Dosage and Selection, White Blood Cell Count

Severe bacterial infection is a common cause of ICU admission. Empiric broad-spectrum, parenteral antibiotic therapy is often initiated based on knowledge of common pathogens and results of Gram staining of appropriate specimens. Culture and sensitivity results should be reviewed when available and empiric antibiotic choices adjusted accordingly. Additionally, critically ill patients are at risk of secondary infections from aspiration pneumonia, indwelling catheters, and bacterial translocation from the gastrointestinal tract. White blood count and differential should be monitored for evidence of new or nonresponsive infections. Culture and sensitivity tests may need to be repeated if patients are not responding to the initial therapy or have signs of secondary infection.

201.4.14 Gastrointestinal Motility and Mucosal Integrity

Ileus predisposes the patient to vomiting and ulceration and should be prevented. Motility can be enhanced with a constant rate infusion of metoclopramide (1 to 2 mg/kg/day). Gastric outflow obstruction must be ruled out before initiating metoclopramide. A nasogastric tube allows accumulated fluid to be suctioned from the stomach and also provides a route for enteral feeding. Enteral feeding provides protection against ulceration. Antiemetic therapy should be considered if vomiting is persistent or is causing significant fluid and electrolyte losses; the recumbent patient is at risk for aspiration.

201.4.15 Drug Dosages and Metabolism

Drug dosages should be reviewed daily. Animals with renal and hepatic dysfunction may have altered metabolism and dosages may need to be adjusted. Interactions among drugs should be considered in animals receiving multiple therapies.

201.4.16 Nutrition

Nutrition is an important and commonly overlooked component of successful management of the ICU patient. These patients rapidly develop a negative energy and protein balance leading to compromised host defenses, loss of muscle strength, visceral organ atrophy and dysfunction, and eventual gastrointestinal barrier breakdown, pneumonia, sepsis, and death. Disuse of the bowel has been implicated as a predisposing factor in bacterial translocation and secondary sepsis, making enteral feeding the preferred route when possible. The nutritional status of critically ill patients should be reviewed daily (see Chapter 202, Nutritional Assessment).

201.4.17 Pain Control

Tachycardia, tachypnea, hypertension, restlessness, mental depression, and poor attitude can be indications of pain. Pain should be controlled not only for the mental well-being of our patients; uncontrolled pain is detrimental to cardiovascular function. Pain is easier to prevent than to treat. Preemptive analgesia should be used for painful conditions and before painful procedures. Patients should be evaluated for pain and the analgesic plan modified accordingly on a continuous basis. Appropriate training of nursing staff is essential to ensure that adequate patient comfort is maintained.

201.4.18 Nursing Care and Patient Mobilization

Recumbent patients should be turned every 4 hours, with passive manipulation of the limbs. Fecal and urine soiling should be prevented. Catheter and tube sites should be inspected daily and care of catheter insertion sites performed appropriately. In patients with multiple lines, labeling can prevent confusion and misuse.

201.4.19 Wound Care and Bandage Change

Incision sites and wounds should be checked several times daily. Wet bandages should be changed immediately. To document progression, skin bruising can be outlined with ink that will not wash off.

201.4.20 Tender Loving Care

Mental health is as important as physical health in our patients. Comfortable, dry bedding, gentle handling by staff members, and visits from owners are important. “Lights out” time when possible will minimize disruption of biorhythms.

201.5 SUGGESTED FURTHER READING*

R Kirby: Septic shock. In JD Bonagura (Ed.): *Current veterinary therapy XII*. 1995, Saunders, Philadelphia, *A chapter that demonstrates the use of a checklist of clinical parameters to guide assessment and therapy of septic shock.*

JM Porter, RR Ivatury: In search of the optimal end points of resuscitation in trauma patients: A review. *J Trauma Inj Infect Crit Care*. **133**, 1998, 908, *An article that reviews the evidence pertaining to physiologic and biochemical markers of occult shock in human trauma patients.*

SD Smarick, SC Haskins, J Aldrich, et al.: Incidence of catheter-associated urinary tract infection among dogs in a small animal intensive care unit. *J Am Vet Med Assoc*. **224**, 2004, 1936, *An article that reports the incidence of urinary tract infection associated with urinary catheterization in a veterinary ICU and recommends a protocol for urinary catheter placement and maintenance to minimize catheter-related infections.*

G Van den Berghe, P Wouters, F Weekers, et al.: Intensive insulin therapy in the critically ill patient. *N Engl J Med*. **345**, 2001, 1359, *A prospective, randomized controlled study that found strict glucose control (at or below 110 mg/dl) significantly reduced morbidity and mortality in human surgical ICU patients.*

* See the CD-ROM for a complete list of references

202 Chapter 202 Nutritional Assessment

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202.1 KEY POINTS

- Nutritional assessment is an important, but often overlooked, aspect of the management of critically ill patients.
- Dietary history, physical examination, and laboratory evaluation are used to determine when, what type, and how much nutritional support to implement for each and every patient.
- All steps in nutritional management should be documented clearly in the medical record.
- All patients should be reassessed daily and changes in nutritional management implemented accordingly.

202.2 INTRODUCTION

It has been estimated that up to 50% of hospitalized small animal patients are malnourished.[1] Malnutrition and wasting contribute to many aspects of critical illness, including impaired immune function, increased susceptibility to infection, delayed wound healing, decreased strength and vigor, and increased morbidity and mortality. Indeed, malnutrition has been implicated as a significant factor that influences outcome in critically ill humans. Therefore prevention of malnutrition by ensuring adequate nutrient intake is crucial in the management of critically ill patients.

It has been well established that nutritional support in critically ill patients will decrease morbidity and mortality, improve tolerance to invasive procedures, shorten hospitalization periods, decrease incidence of infections, enable earlier ambulation, hasten wound healing, and reduce complications. When to initiate nutritional support requires early assessment of the patient to identify those either at risk of malnutrition or those who already require nutritional support.

In humans, a technique referred to as *subjective global assessment (SGA)* is used to assess the nutritional status of patients.[2] The SGA uses information from the history and physical examination to screen for malnutrition. The SGA classification technique uses historical data on weight change, dietary intake, gastrointestinal signs influencing oral intake and absorption, or any effects of undernutrition that may impact functional capacity. A physical examination is performed to detect clinical characteristics of undernutrition, such as muscle wasting, loss of subcutaneous tissue, edema, or ascites. These results are used collectively to categorize the patient as well nourished (classification A), mild or moderately (or suspected of being) malnourished (classification B), or severely malnourished (classification C).

The SGA is a well-validated tool for screening for malnutrition in a variety of conditions including transplantation, hepatic disease, cancer, and geriatric care. Although subjective, its simplicity allows it to be used by all of the medical staff. The SGA is the only screening tool recommended by the American Society for Parenteral and Enteral Nutrition.[3] Although no such standardized scoring system exists in veterinary medicine, the principles of SGA can be applied to ensure that appropriate history, physical examination, laboratory data, and diagnostic techniques are applied for the assessment of veterinary patients with or at risk of malnutrition.

202.3 HISTORY

The dietary history should record if the patient is or is not consuming food. If not, then the duration of inappetence or anorexia should be recorded. It is important to record the total duration of inappetence, that is, the number of days the pet was inappetent both in the home before hospitalization and in the hospital. If the patient is consuming food, the name, the manufacturer, the type (dry, wet, semi-moist), the amount fed each day (cans or standard 237-ml cups), the frequency of food intake, and the method of feeding (ad libitum versus meal feeding) should be recorded.

It is also important to differentiate between how much food the pet is offered versus how much of the food is consumed. For example, the client or hospital staff may “feed” the pet 2 cups of food twice a day. This information is meaningless without knowing if the pet actually eats the full 2 cups twice a day. It is vital to know both how much food typically is offered, and how much food is actually consumed. The person responsible for feeding should be identified because this may not be the person presenting the pet for examination; knowing this may help to verify or refute the accuracy of the dietary information provided. The number and type of snacks or human foods that are offered each day and potential access to other pets food (indoor or outdoor) should be determined. Allergies, sensitivities, and intolerances to food should be ascertained. The history should also be explored to fully understand when the current diet was implemented and any changes in the diet or dietary intake that have occurred recently.

The incidence of vomiting or diarrhea should be noted. Injuries that prevent adequate oral intake (facial injuries, prolonged or unmanaged pain, injuries requiring surgical correction) and conditions of excessive protein loss (peritoneal drainage, open discharging skin wounds, protein-losing enteropathy) should be recorded. Nutritional assessment should also identify factors that can impact the nutritional plan such as cardiovascular instability; gastrointestinal, pancreatic, hepatic, or renal failure; fluid, electrolyte, or acid-base abnormalities; hyperglycemia; or hypertriglyceridemia.

202.4 BODY WEIGHT

The body weight should be included in the examination of every patient. Body weight provides a rough measure of total body energy stores, and changes in weight typically parallel energy and protein balance. In the healthy animal, body weight varies little from day to day. However, additional challenges may arise in the critically ill patient. Edema and ascites cause a relative increase in extracellular fluid and may mask losses in chemical or cellular components. Conversely, massive tumor growth or organomegaly can mask loss of fat or lean tissues. There can also be wide variation among scales, so it is important to use the same one for an individual animal to prevent interscale variation.

A single body weight measurement by itself has little meaning. For example, knowing that a patient weighs 30 kg does not tell you if it is underweight, normal weight, or overweight. Therefore it is also important to know if the patients' body weight has changed recently and how rapidly it has changed, that is, over several days, weeks, or months. Rapid changes in body weight are likely to be associated with significant loss of lean body mass. Therefore body weight should not be used in isolation and can be altered falsely by dehydration or fluid accumulation.

Body weight can be subdivided into two or more physiologically distinct components. The traditional two-compartment model divides body weight into the fat mass (FM) and the fat-free mass (FFM).[4] This model forms the basis of most of our knowledge of body composition and is dependent on assumptions regarding the character of the FM and the FFM. The composition of the FFM is assumed to be relatively constant, with a density of 1.1 g/

cc at 37°C, a water content of 72% to 74%, and a potassium content of 50 to 70 mmol/kg.[5] In addition, the major constituents of the FFM are presumed to be present in fixed ratios. In comparison, the FM is relatively homogenous in composition, anhydrous, and potassium free, with a density of 0.9 g/cc at 37°C.

Assessment of body composition in the form of FM and FFM provides valuable information about the physical and metabolic status of the individual. The FM can be considered to represent a calorie or energy storage depot. Conversely, the FFM represents the actual health of the animal. It is a heterogenous entity consisting predominantly of intracellular fluid (ICF) and extracellular fluid (ECF), minerals, glycogen, and protein. The FFM contains the body cell mass (BCM), the metabolically active part of the body responsible for determining most of the resting energy expenditure. BCM encompasses those lean tissues most likely to be affected by nutrition or disease over relatively short periods. Furthermore, the FFM generally is accepted as an index of protein nutrition, so changes in FFM are assumed to represent alterations in protein balance.

202.5 BODY CONDITION SCORE

The body condition score (BCS) provides a quick, reliable, and subjective assessment of an animal's overall body condition. The BCS focuses on body fat. The two most commonly used scoring systems in small animal practice are a 5-point system in which a BCS of 3 is considered ideal, or a 9-point system in which a BCS of 5 is considered ideal. The BCS in conjunction with body weight gives a clinician a more complete perspective on a patient's body condition. Limitations of the BCS include the subjectivity inherent in the scoring system and interobserver variation. Finally, like body weight, BCS gives an overall assessment of body condition; it cannot differentiate between body compartments and does not provide any precise quantitative information concerning alteration in FFM or lean body mass relative to fat mass.

202.6 MORPHOMETRIC MEASUREMENTS

Height and circumferential measurements of the abdomen, hip, thigh, and upper arm are used commonly to estimate nutritional status in humans. Circumferential measurements have also been developed to estimate the percent body fat in cats.[6] The Feline Body Mass Index is determined by measuring the rib cage circumference at the level of the ninth cranial rib and the leg index measurement (LIM), which is the distance from the patella to the calcaneal tuber. The measurements must be obtained in centimeters. The percent body fat can be calculated using a simplified equation of FM (%) = 1.5(ribcage – LIM) – 9. Pelvic circumference and distance from hock to stifle has been shown to predict body fat in dogs.[7]

Measurement of skinfold thickness has been used extensively in humans to determine the percentage of body fat using equations derived for various populations. This estimate is based on the relationship between thickness of subcutaneous fat layer and total body fat. Unfortunately, these measurements cannot be used in dogs and cats because canine and feline skin is easily detached from underlying fat tissue, which makes skinfold measurement impractical and unreliable.

Another method of measuring the subcutaneous fat layer is ultrasonography. This technique has been used experimentally in Beagles, and equations have been derived to predict the percentage of body fat from the subcutaneous fat thickness.[8] These regression equations do not work in other dog breeds, but future research may allow investigators to develop new, more accurate equations for this simple technique.

202.7 CACHEXIA MEASUREMENTS

In many critically ill patients the weight loss is disproportional such that there is substantially greater loss of the metabolically active lean body mass than fat mass. This condition has been termed *cachexia*. In humans, skeletal muscle mass can be predicted by the circumference of the midarm muscle, the midarm muscle area, or the creatinine-height index. To the authors' knowledge, such techniques have not yet been reported for cats or dogs. In dogs, initial loss of lean body mass can be subtle and is usually first noted in the epaxial, gluteal, scapular, or temporal muscles. A subjective cachexia scoring system will facilitate the identification of those patients with either cachexia or impending cachexia (Table 202-1).[9]

The major by-product of protein catabolism is urea. Therefore the rate of protein catabolism can be estimated by determining the amount of urea nitrogen excreted each day. The total protein loss and protein balance can be calculated from the urinary urea nitrogen in hospitalized dogs.[10] The technique is, however, time consuming and requires urine collection for 24 hours.

202.8 BIOELECTRICAL IMPEDANCE ANALYSIS

Bioelectrical impedance analysis (BIA) is an electrical method of assessing body composition that has the potential of quantifying total body water, extracellular water, intracellular water, BCM, FFM, and FM. Electrical conductance is used to calculate the composition of the body by measuring the nature of the conductance of an applied electrical current in the patient. Body fluids and electrolytes are responsible for conductance, and cell membranes produce capacitance. Because adipose tissue is less hydrated than lean body tissue, more adipose tissue results in a smaller conducting volume or path for current and larger impedance to current passage. The FFM contains virtually all the water in the body, so if bioelectrical impedance is measured, a value for FFM can be determined.

Table 202-1 Cachexia Scoring System

Cachexia Score	**Description**
0	Good muscle tone with no evidence of muscle wasting
1	Early, mild muscle wasting, especially in the hindquarters and lumbar region
2	Moderate muscle wasting apparent in all muscle groups
3	Marked muscle wasting as evidenced by atrophy of all muscle groups
4	Severe muscle wasting

Modified from Freeman LM: *Nutritional modulation of cardiac disease,* London, 2000, WALTHAM Focus Special Edition Advances in Clinical Nutrition.

Two types of BIA systems are available; the single-frequency type applies a 50-kHz current, and the multifrequency type uses frequencies from 5 to 1000 kHz. A BIA test is performed by placing four small electrodes on the body. The electrical current is introduced into the patient from the distal electrodes. As the current travels through the body it experiences a slight delay due to cells, and the current is then detected by proximal electrodes. Low frequencies (e.g., 5 kHz) pass primarily through the extracellular water because of high cell membrane capacitance. In contrast, at higher frequencies the effects of cell membrane capacitance is diminished, so that the current flows through both the ICF and ECF environments (or total body water). The proportion of the current in the ICF and ECF is frequency dependent.

BIA may be affected by hydration status, consumption of food and water, skin and air temperature, recent physical activity, conductance of the examination table, patient age, size, shape, and posture, in addition to electrode positioning. Reliable BIA requires standardization and control of these variables. BIA been shown to be a safe, noninvasive, rapid, portable, and reproducible method to estimate body composition in healthy dogs, cats, and humans.[11,12] BIA has been used to effectively determine body cell mass in critically ill patients.[13] Robert and others reported that changes in body cell mass significantly correlated with changes in protein and energy intake in critically ill humans.[14] Calculation of ECF and ICF (and subsequent calculation of total body water, FM, FFM, and BCM) takes approximately 1 minute, hence BIA provides instantaneous on-line information of body composition that has never before been available. Further studies are required to determine the efficiency of BIA to facilitate daily changes in nutritional assessment of critically ill canine and feline patients.

202.9 LABORATORY INDICATORS OF MALNUTRITION

Laboratory indicators of malnutrition include hypoalbuminemia, decreased blood urea nitrogen levels, hypocholesterolemia, anemia, and lymphopenia. However, alterations of these common laboratory indicators of malnutrition are often indistinguishable from those that can occur with concurrent disease. Fascetti and others reported that anorectic cats have significantly higher serum creatinine kinase concentrations than do healthy cats.[15] Furthermore, the creatinine kinase concentration significantly decreased within 48 hours of implementation of nutritional support. Creatinine kinase may serve as a useful indicator of anorexia in cats. Other markers of nutritional status, including prealbumin, transferrin, total iron-binding capacity, fibronectin, retinal binding protein, ceruloplasmin, α_1-antitrypsin, α_1-acid glycoprotein, and C-reactive protein, have not been fully evaluated in feline and canine patients.

202.10 INTEGRATING THE DATA

The most important function of the critical care specialist is to ensure that all patients, regardless of the diagnosis, are adequately nourished. Not only must the normal nutritional requirements of the healthy pet be considered, but the nature of the pet's illness must be taken into account and nutrients modified accordingly. All steps in nutritional management should be documented completely and clearly in the medical record. Accurate documentation facilitates communication among the various members of the veterinary care team and strengthens the importance of nutrition in the overall care of the patient. Indeed, the problem-oriented approach can be used for nutritional support to ensure that all of the patient's metabolic and nutritional problems are documented clearly, assessed, and planned for. The importance of clear documentation is exemplified by the study of 276 dogs in which a negative energy balance occurred in 73% of the hospitalization days.[1] The negative energy balance was attributed to poorly written orders in 22% of cases.

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Nutritional assessment is not used to determine who should be fed and who should not. Rather it is used to determine how much food, which type of food, and the most effective way to feed the patient. The dietary history should be used to calculate the total daily caloric intake of the pet, and this value compared with the calculated daily caloric requirement. In critically ill patients, it is generally recommended that the patient at least consume the resting energy requirements, which can be calculated as $70 \times \text{BW (kg)}^{0.75}$. If the patient is not voluntarily consuming adequate calories, nutritional intervention in the form of enteral or parenteral nutrition is required.[16]

Indications for nutritional support include a history of illness or weight loss, current poor body condition or acute loss of more than 5% body weight, or a history of anorexia or inappetence for more than 3 days (real or anticipated). Regardless of the method of nutritional support selected, it is imperative to assess the effect of the support frequently, making nutritional assessment a cyclic process.

202.11 SUGGESTED FURTHER READING*

KE Michel, LG King, E Osro: Measurement of urinary urea nitrogen content as an estimate of the amount of total urinary nitrogen loss in dogs in intensive care units. *J Am Vet Med Assoc*. **210**, 1997, 356, *Clinical study validating the use of urinary urea nitrogen content to estimate total urinary nitrogen content in critically ill dogs*.

RL Remillard, DE Darden, KE Michel, et al.: An investigation of the relationship between caloric intake and outcome in hospitalized dogs. *Vet Ther*. **2**, 2001, 301, *Prospective multicenter clinical study evaluating the feeding orders and nutritional management of critically ill hospitalized dogs*.

* See the CD-ROM for a complete list of references

203 Chapter 203 Hemodynamic Monitoring

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203.1 KEY POINTS

- Hemodynamic monitoring is essential in the treatment of many critically ill patients because it is important in guiding fluid and pharmacologic therapy to optimize cardiovascular function.
- Monitoring options include physical examination parameters, continuous electrocardiogram (ECG) and blood pressure monitoring, central venous pressure (CVP) monitoring, pulmonary artery pressure monitoring, and other technologies to measure cardiac output.
- Continuous ECG monitoring can detect intermittent arrhythmias and enable the clinician to monitor the need for treatment based on the rate and rhythm.
- CVP is relatively easy to monitor and can guide fluid therapy, particularly in patients that are hypovolemic or have septic shock, heart disease, or renal disease.
- Cardiac output monitoring can be performed in dogs and cats. A variety of techniques are available, including thermodilution, lithium dilution, pulse contour analysis, and carbon dioxide rebreathing.

203.2 INTRODUCTION

Hemodynamic monitoring can range from basic physical examination parameters, to continuous electrocardiogram (ECG) and blood pressure monitoring, to central venous pressure (CVP) monitoring, and to the most advanced forms including pulmonary artery pressure (PAP) monitoring and other technologies to measure cardiac output, cardiac index, systemic vascular resistance, oxygen delivery, and oxygen uptake. The type of monitoring chosen will depend on the severity of illness as well as the clinician's comfort with the various modalities.

203.3 CONTINUOUS ELECTROCARDIOGRAM

Continuous ECG monitoring can be very useful in critically ill patients; it provides continuous, hands-off access to the heart rate and rhythm. It allows for the clinician to catch arrhythmias that may be intermittent and infrequent, and monitor the need for treatment based on the rate and rhythm. Both standard and telemetric systems are available, with the telemetry models allowing for easier patient movement and less tangling and disconnection of the leads required by the standard systems.

203.4 BLOOD PRESSURE MONITORING

Blood pressure monitoring is extremely useful in critical cases. It allows fluid therapy to be tailored to a patient's needs when used along with physical examination parameters, urine output, and even CVP monitoring. It is essential in guiding the use of inotropic agents and pressors, and these therapies should not be used unless blood pressure can and will be measured frequently. Normal blood pressure values for dogs are systolic pressures of 110 to 190 mm Hg and diastolic pressures of 55 to 110 mm Hg. For cats, normal ranges are 120 to 170 mm Hg for systolic and 70 to 120 mm Hg for diastolic. Mean arterial blood pressure (MAP) can be calculated from these measured values as follows:

$$\text{MAP} = \text{diastolic} + {}^{1}\!/_{3}\,(\text{systolic} - \text{diastolic})$$

Hypotension is defined as systolic blood pressure less than 80 mmHg or mean arterial pressure of less than 60 mmHg in either species. Causes of hypotension include decreased cardiac output secondary to reduced circulating volume, myocardial failure, severe bradyarrhythmia or tachyarrhythmia, or decreased systemic vascular resistance due to peripheral vasodilation secondary to sepsis or systemic inflammatory response syndrome. Treatment of hypotension should always be aimed at correcting the underlying problem (see Chapter 6, Hypotension).

Hypertension can be primary (essential hypertension), which is rare in both cats and dogs, or secondary from another disease process that alters renal or neurohormonal function. Renal failure, acute or chronic, is the most frequent cause of secondary hypertension, but hyperthyroidism, diabetes mellitus, hyperadrenocorticism, pheochromocytoma, and various medications (glucocorticoids, cyclosporin A, phenylpropanolamine, and erythropoietin) have also been associated with hypertension.

Blood pressure monitoring can be divided into two main categories, noninvasive and invasive methods. The noninvasive methods are used most commonly, and in veterinary patients they usually consist of either the oscillometric or Doppler methods, although photoplethysmography is also available. Invasive blood pressure monitoring provides direct arterial pressure measurement and is the most accurate method available.

203.4.1 Noninvasive Blood Pressure Monitoring

Noninvasive blood pressure monitoring is based on inflation of a cuff to occlude arterial flow, followed by measurement of the pressure at which flow returns. These methods are technically easy to use and require relatively inexpensive equipment but are prone to error, usually due to selection of an inappropriate cuff size. The guideline for the cuff width is approximately 40% of the circumference of the limb for dogs and 30% of the circumference of the limb for cats. If the cuff is too small, a falsely high pressure will be obtained; if the cuff is too large, a falsely low reading will result.[1]

The Doppler method measures only systolic pressure and usually is used in smaller animals such as cats, very small dogs, and exotic species. It is also useful in patients with hypotension or those that have arrhythmias because the Dinamap (device for indirect noninvasive automatic mean arterial pressure) is commonly inaccurate or does not give any readings at all in these circumstances. The Doppler method uses a 10-MHz ultrasound probe to detect blood flow in an artery. The probe is placed over an artery distal to the cuff. Doppler sounds become audible when pressure in the cuff is less than the pressure in the artery. Although the Doppler typically is regarded as measuring the systolic pressure, one study that compared Doppler readings with direct blood pressure monitoring in anesthetized cats found that the Doppler consistently underestimated systolic pressures by 10 to 15 mm Hg and was more closely correlated to MAP. This study was only in anesthetized healthy cats, so limitations are present.[2]

The Dinamap uses an oscillometric method of blood pressure determination. The cuff is alternately inflated and deflated, and during deflation alterations in cuff pressure are sensed by the transducer. These oscillations are caused by pulses in the limb. The peak amplitude of oscillations equals the mean arterial pressure. Systolic pressure equals the pressure at which oscillations are first detected, and diastolic pressure equals the pressure at which oscillations decrease rapidly.

Many machines calculate systolic and diastolic blood pressure from the mean arterial pressure using built-in algorithms, making the mean arterial pressure the most accurate value. The heart rate is measured as the number of oscillations occurring per minute, and should always be compared with the patient's heart rate as determined manually or by ECG. The Dinamap has been evaluated in anesthetized and awake dogs and found to have reasonable accuracy in the normotensive ranges.[3–6] The Dinamap is not reliable in cats[7] or very small dogs, and even in appropriately sized patients errors can result if the patient moves or if significant arrhythmias are present. A similar device, the Cardell, also determines systolic, diastolic, and mean pressures and has been accurate in cats as well as dogs, eliminating some of the concerns associated with the Dinamap.[8]

203.4.2 Photoplethysmography

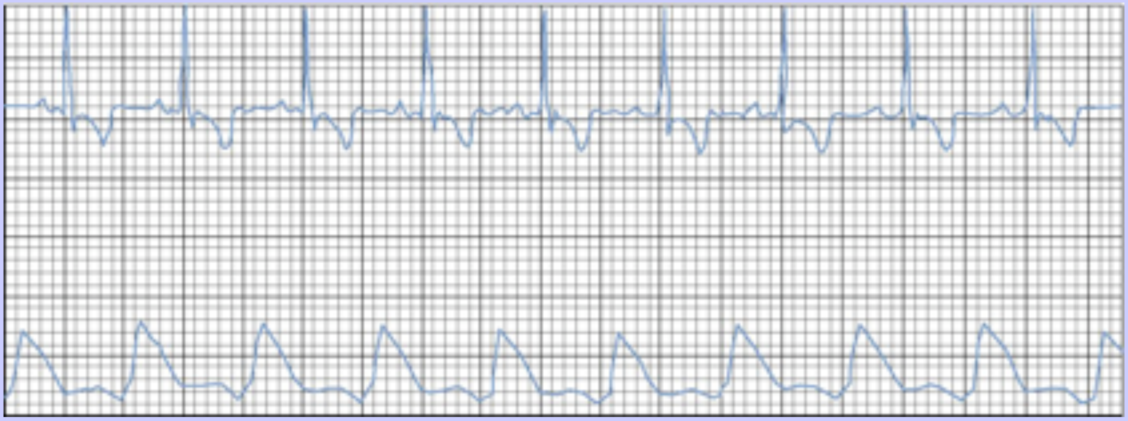
Originally designed for use on the human finger, this method is based on the "volume clamp" principle. The blood volume of an extremity varies in a cyclic pattern with each cardiac cycle. The variation is detected by a photoplethysmograph attached to a finger (or on the foot or tail in veterinary patients). If the cuff is inflated and deflated fast enough to maintain a constant volume in the finger (or distal extremity), the cuff pressure will equal intraarterial pressure. This allows for a constant, real-time display of cuff pressure, and therefore intraarterial pressure, and measurement of systolic and diastolic pressures.[9] It has been evaluated in dogs and cats and found to be accurate but has not come into common use.[2,7]

203.4.3 Invasive Blood Pressure Monitoring

Invasive or direct arterial blood pressure monitoring is considered the gold standard for blood pressure measurement in both veterinary and human patients, awake and anesthetized. It is usually performed after inserting an arterial catheter that is connected to a pressure transducer and monitor, allowing for continuous monitoring of systolic, diastolic, and mean pressures. Techniques for direct arterial puncture and single-pressure measurement have also been described.

When a display monitor is employed, continuous direct arterial pressure monitoring allows for observation of pressure changes and trends (Figure 203-1). Another advantage of an arterial catheter is that it can be used to obtain blood samples for arterial blood gas analysis and laboratory testing. Despite its many advantages, direct monitoring should be limited to critically ill patients that will benefit from having their blood pressure measured 860 frequently over a defined period, such as during anesthesia in a patient with a high anesthetic risk or while 861 hospitalized in an intensive care unit.

Figure 203-1 Direct arterial blood pressure waveform and continuous electrocardiogram. Note that one arterial pressure waveform is seen just after completion of each cardiac complex.



Direct arterial blood pressure monitoring in patients with hypovolemic or septic shock is extremely helpful in guiding volume replacement and the use of pressors to maintain an acceptable systemic blood pressure. By evaluating the pressure waveform with various arrhythmias, the clinician can distinguish which ones are causing poor pressures or even pulse deficits, and this can influence the decision as to whether or not to initiate treatment. Direct arterial blood pressure monitoring is not indicated in active, relatively healthy patients because of possible morbidity from arterial catheter placement and risk of the patient pulling the catheter out or disconnecting the arterial line and causing significant hemorrhage. Animals with arterial catheters must be strictly supervised at all times (see Chapter 49, Arterial Catheterization).

Once an arterial catheter is placed, it is connected to semirigid tubing that has been primed with heparinized saline from a bag of 0.9% sodium chloride with 1 unit of heparin per milliliter of saline. The fluid bag is pressurized to 300 mm Hg to prevent backward flow of arterial blood into the tubing. The tubing from the catheter is attached to a pressure transducer that is connected to a cable and mounted on a board placed at the level of the patient's heart. The pressure transducer converts the pressure changes into an electrical signal that is carried to the monitor by the transducer cable, and then the signal is amplified and displayed on a monitor as a pressure waveform, showing the peak systolic pressure, dicrotic notch (which is created by closure of the aortic valve), and diastolic pressure. Monitors will also display numeric values for the systolic, diastolic, and mean arterial pressures.

Although direct arterial monitoring is considered the gold standard for blood pressure monitoring, it can give erroneous results if compliant tubing is used, the catheter is lodged up against the arterial wall, a clot forms at the tip of the catheter, air bubbles are present in the catheter or tubing, or the catheter or tubing becomes kinked. All of these problems can result in the waveform becoming damped, giving lower systolic and higher diastolic values than are present. Direct arterial blood pressure monitoring has higher associated morbidity than do noninvasive methods, including hematoma formation at the site of arterial puncture, infection, thrombosis of the artery, or necrosis of the tissues distal to the catheter (particularly in cats that have an indwelling catheter for more than 6 to 12 hours). Keeping the arterial line patent requires heparinization of the line and catheter, which can be of concern in very small patients. Fortunately, all of the complications other than hematoma formation are quite rare.

203.4.4 Telemetric Blood Pressure Monitoring

Telemetric units are available for implantation into dogs and potentially cats (Data Sciences International, St. Paul, MN). These require surgical implantation of a transmitting device that sends digital information to a receiver that can either be collected by a computer and evaluated later or converted into an analog signal for recording on a strip chart.

The device is placed subcutaneously, and has a polyurethane catheter with an antithrombogenic coating and a biocompatible gel at the end that is fed into the femoral artery. This technology has been used in laboratory settings for a number of years and is being used in a number of trials in both feline and canine patients. These devices allow for free patient movement and prevent the stress of handling and restraint from affecting the blood pressure measurements obtained. These are not used commonly in clinical patients but may be a viable option in the future for those that require long-term hospitalization or repeated blood pressure monitoring.

203.5 CENTRAL VENOUS PRESSURE MONITORING

CVP is the hydrostatic pressure in the intrathoracic vena cava, and in the absence of a vascular obstruction is approximately equal to right atrial pressure. When the tricuspid valve is open, right atrial pressure equals right ventricular end-diastolic pressure. This pressure is used to estimate right ventricular end-diastolic volume and the relationship between blood volume and blood volume capacity. It also gives a measure of the relative ability of the heart to pump the volume of blood that is returned to it. Patients that are hypovolemic or have septic shock, heart disease, or renal disease (especially oliguric or anuric renal failure) can benefit from CVP monitoring.

CVP monitoring requires a central venous catheter, usually a 16-gauge or 19-gauge jugular catheter, but a femoral vein catheter that extends into the abdominal vena cava has been shown to accurately measure CVP in cats (without significant intraabdominal disease[10]) and in puppies.[11] The size of the catheter has no effect on measurement of CVP.[12]

The tip of the catheter should be positioned in the cranial or caudal vena cava just outside of the right atrium. The catheter is then connected to a 3-way stopcock via noncompliant tubing, and to a manometer containing heparinized saline or to a pressure transducer as described above for direct arterial blood pressure monitoring. The central catheter can be used for CVP monitoring and can also serve for fluid administration or intermittent blood sampling. However, if the CVP is to be monitored continuously and the patient requires additional venous access, a multilumen catheter can be used so that the other ports remain available for fluid therapy, infusions, and blood sampling. Double-lumen and triple-lumen catheters are available in a variety of sizes and lengths (see Chapter 63, Central Venous Catheterization).

When connecting the central venous catheter to the system, the zero reference point for the bottom of the manometer or the pressure transducer should be the manubrium for a patient in lateral recumbency or the point of the shoulder for a patient in sternal recumbency. Normal ranges for CVP are 0 to 5 cm H_2O, but they can vary in individual animals.[13] This makes trends in the CVP much more significant than individual readings. Values can be affected by patient position, so a consistent position should be used when comparing values. Catheter position will also affect readings and can be confirmed by radiography or fluoroscopy.

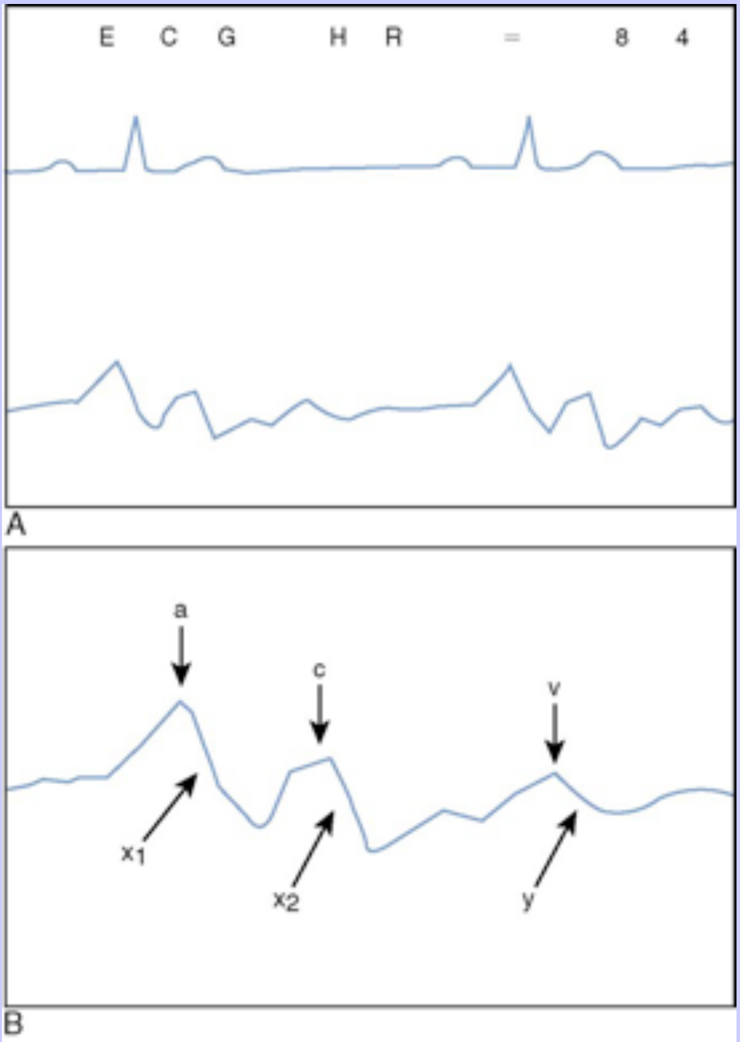
The CVP will vary throughout the respiratory and cardiac cycles because CVP reflects right atrial pressure. During inspiration, intrathoracic pressure decreases and the CVP will fall. The reverse will occur during exhalation. If a patient has an upper airway obstruction and difficulty inspiring, these changes will be exaggerated. Positive-pressure ventilation will reverse this pattern.

The complexity of the CVP waveform can be seen when it is displayed on a monitor, and the variations that occur during the cardiac cycle can be observed (Figure 203-2, *A* and *B*). Three positive waves are seen: *a, c,* and *v* waves, and two negative depressions: *x* and *y* descents. The *a* wave represents the increase in the CVP caused by right atrial contraction. The *c* wave is caused by bulging of the tricuspid valve into the right atrium, increasing right atrial pressure and CVP as the right ventricle contracts. The *x* descent is caused by decreased atrial pressure during ventricular ejection. The *v* wave is caused by increasing pressure from blood flowing into the right atrium before the tricuspid valve opens. The *y* descent represents rapid emptying of the right atrium as the tricuspid valve opens, allowing blood to flow into the right ventricle. Careful evaluation of the waveform will allow abnormalities in each part of the cycle to be detected and differential diagnoses to be considered; for example, large *c* waves are often associated with tricuspid regurgitation.[14,15]

A low CVP (less than 0 cm H_2O) indicates hypovolemia due to fluid loss or vasodilation secondary to decreased peripheral venous resistance. A high CVP (greater than 10 cm H_2O) may indicate volume overload, right-sided heart failure, or significant pleural effusion.[16,17] CVP readings of greater than 16 cm H_2O often lead to edema formation or body cavity effusions. Some causes of right-sided dysfunction include right-sided myocardial failure, pericardial effusion and tamponade, restrictive pericarditis, and volume overload from excessive intravenous fluid administration.

If a CVP reading is questionable, a small test bolus of an isotonic crystalloid such as 0.9% saline or a balanced electrolyte solution can be used. A bolus of 10 to 15 ml/kg of crystalloid or 5 ml/kg of colloid is given over 5 minutes or less. The vascular bed is a very compliant system, able to accommodate changes in volume with minimal changes in pressure. If the patient has a low CVP due to hypovolemia, the CVP will either show no change or will have a transient rise toward normal, then rapidly decrease again. The mean arterial pressure may also increase with the test bolus and return toward prebolus measurements. A small increase of 2 to 4 cm H_2O with a return to baseline within 15 minutes is usually seen with euvolemia. A large increase (greater than 4 cm H_2O) and slow return to baseline (more than 30 minutes) is seen with hypervolemia or reduced cardiac compliance.[17]

Figure 203-2 **A,** Central venous pressure (CVP) waveform and continuous electrocardiogram. Each phase of the cardiac cycle is reflected in the CVP waveform. **B,** CVP waveform with waves and depressions labeled. *a* = *a* wave, represents the increase in the CVP caused by right atrial contraction; *c* = *c* wave, caused by bulging of the tricuspid valve into the right atrium; *v* = *v* wave, caused by increasing pressure from blood flowing into the right atrium before the tricuspid valve opens; x_1 = x_1 descent; x_2 = x_2 descent, caused by decreased atrial pressure during ventricular ejection; *y* = *y* descent, represents rapid emptying of the right atrium as the tricuspid valve opens.



Contraindications for CVP measurement are few and relate to central venous catheter placement. These include coagulopathies that would make puncture of the jugular or femoral vein an unacceptable risk; high risk of thromboembolic disease including animals with protein-losing nephropathy, hyperadrenocorticism, or immune-mediated disease; or when increased intracranial pressure is a risk such as in patients with head trauma, seizures, or intracranial disease.

The biggest limitation of CVP is that it measures the pressures on the right side of the heart instead of the left side 862
because it is the left side that supplies the systemic circulation and drains the pulmonary circulation. Pressures in 863
the left side are more accurate in guiding fluid therapy, but they require a pulmonary artery catheter, which is much more expensive, time consuming, and technically challenging. This makes CVP much more available and an acceptable alternative to PAP and pulmonary artery occlusion pressure (PAOP) monitoring.

203.6 PULMONARY ARTERY PRESSURE MONITORING

PAP monitoring requires that a catheter be placed in the jugular vein, through the right atrium and ventricle, and into the pulmonary artery. A pulmonary artery catheter allows for measurement of the systolic, diastolic, and mean PAP (see Chapter 50, Pulmonary Arterial Catheterization). If it is equipped with a balloon, PAOP (also called the *pulmonary wedge pressure*) can be measured when the balloon at the end of the catheter is inflated in a distal branch of the pulmonary artery. Inflation of the balloon eliminates PAP created by blood flow, and the measured pressure reflects the left atrial filling pressure as it equilibrates across the pulmonary capillary bed.

When the mitral valve is open, left atrial pressure equals left ventricular end-diastolic pressure. This pressure provides the best measure of left ventricular preload and is the best predictor of pulmonary edema secondary to fluid overload. Preload is the amount of stretch in the ventricle at the end of diastole and is an important determiner of cardiac output.

Similar to CVP, PAP and PAOP can be used (and are more accurate) to determine the fluid volume status of a patient. Normal PAOP in dogs is 5 to 12 mm Hg.[18] Low PAOP usually represents volume depletion and a patient that will benefit from fluid administration, and increased PAOP is indicative of volume overload or cardiac dysfunction in patients for which additional fluid is contraindicated.

Additional parameters that can be monitored with a Swan-Ganz type catheter are right atrial pressures (used in place of CVP), which are measured via the proximal port of the catheter, and cardiac output, which is determined by thermodilution technique (thermodilution cardiac output [TDCO]). A known quantity of solution (either saline or 5% dextrose) at a known temperature is injected rapidly into the proximal port of the catheter. The cooler solution mixes and cools the surrounding blood, and the temperature difference is sensed by a thermistor at the distal tip of the catheter. The change in temperature is plotted on a time-temperature curve. The area under the curve is inversely proportional to the cardiac output, which is calculated by a cardiac output monitor. Normal values for cardiac output are 125 to 200 ml/kg/min for dogs and 120 ml/kg/min for cats.[18,19]

Other values that can be calculated include cardiac index (cardiac output ÷ body surface area [m^2]), stroke volume (cardiac output ÷ heart rate), stroke volume index (stroke volume ÷ body surface area), systemic vascular resistance ([mean arterial pressure − right atrial pressure] ÷ cardiac index), and pulmonary vascular resistance ([mean PAP − PAOP] ÷ cardiac index).[19] Some catheters are also equipped with an oximeter that will measure central venous hemoglobin saturation (SvO_2). This information, combined with the arterial oxygen saturation (SaO_2), allows for the determination of oxygen content of both arterial and mixed venous blood, oxygen delivery, oxygen consumption, and oxygen extraction (see Chapter 212, Cardiac Output Monitoring).

Placement of these catheters is not without risk because arrhythmias, damage to the tricuspid and pulmonic valves, rupture of a pulmonary artery, and pulmonary thromboembolism have all been reported in humans undergoing the procedure.[20]

203.7 TRANSPULMONARY THERMODILUTION CARDIAC OUTPUT

Transpulmonary thermodilution (PiCCO, Pulsion Medical Systems, Munich, Germany), like pulmonary arterial TDCO, utilizes the principle of temperature change following injection of iced saline and the conservation of thermal energy to calculate cardiac output. However, unlike pulmonary arterial TDCO, which requires a pulmonary arterial catheter, the PiCCO system requires only a central venous catheter and a peripheral thermistor-tipped arterial catheter. Cardiac output and other hemodynamic variables, including systemic vascular resistance, global ejection fraction, and global end-diastolic volume, can be obtained from an injection of iced saline into the central venous catheter, with the temperature change detected at the peripheral arterial catheter. This method does not have the associated complications of a pulmonary arterial catheter and has been validated in humans but it has been validated only in dogs that have had a thermistor-tipped catheter placed in the femoral artery following a cutdown. Validation of the technique with a percutaneous insertion of the catheter into the dorsal pedal artery is under way.

203.8 LITHIUM DILUTION CARDIAC OUTPUT MONITORING

Lithium dilution cardiac output monitoring (LiDCO, Cambridge, UK) is an example of indicator dilution cardiac output. Instead of using a change in temperature to calculate cardiac output, an indicator is injected into the venous circulation and the amount of dilution of this indicator in the arterial circulation is measured over time. The dilution of this indicator is then used to calculate cardiac output and other hemodynamic variables. Unlike TDCO, this does not require a pulmonary arterial catheter with the inherent risks listed above.

The LiDCO method is performed by injecting lithium chloride into a central or peripheral venous catheter. Blood is withdrawn from an existing arterial catheter past a lithium sensor using a peristaltic pump. The sensor is connected to a LiDCO monitor that analyzes the lithium dilution time curve and calculates cardiac output. It has been validated as an accurate measurement of cardiac output compared with TDCO in humans, horses, pigs, and dogs.[21] It does, however, require sampling a large volume of blood for repeated measures of cardiac output, which limits its use in small animal practice. Potential side effects of lithium in small animals have also created concern. Indocyanine green has also been used for indicator dilution–derived cardiac output, but is not used clinically in humans because of the potential for allergic reactions.

203.9 PULSE CONTOUR CONTINUOUS CARDIAC OUTPUT MONITORING

This methodology derives cardiac output from analysis of the arterial pressure waveform to give a real-time assessment of a patient's hemodynamic status. It is available with the PiCCO (Pulsion Medical Systems, Munich, Germany) and LiDCO Plus (LiDCO, Cambridge, UK) systems, following initial calibration by thermodilution or lithium dilution as described for the two techniques above. Calibration involves the calculation of aortic impedance, which is used in the algorithm together with the area under the curve of the arterial pulse wave to derive continuous measurements of cardiac output and other hemodynamic variables. The area under the curve minus aortic impedance is equal to the calculated stroke volume, and cardiac output is determined by multiplying the stroke volume by the heart rate. Cardiac output obtained using the LiDCO Plus system has been validated in dogs.[22]

203.10 ALTERNATIVE METHODS FOR CARDIAC OUTPUT MONITORING

Partial carbon dioxide rebreathing has been used to develop a newer modality based on a variation of the Fick principle. This method has been validated in dogs[23] but is not as useful in small dogs or cats because of the size of the breathing circuit required. Other methods that have been investigated include transesophageal echocardiography and bioimpedance. Unfortunately, these have not been very accurate or reliable in small animals.

203.11 SUGGESTED FURTHER READING*

SH Binns, DD Sisson, DA Buoscio, DJ Schaeffer: Doppler ultrasonographic, oscillometric sphygmomanometric, and photoplethysmographic techniques for noninvasive blood pressure measurement in anesthetized cats. *J Vet Intern Med*. **9**, 1995, 405, *This paper compared Doppler, Dinamap, and photoplethysmography (Finapres) methods with direct arterial blood pressure monitoring in anesthetized cats, and found the Dinamap to be the least accurate method, and the Doppler method the most accurate of the indirect methods*.

B Hansen: Technical aspects of fluid therapy. In SP DiBartola (Ed.): *Fluid therapy in small animal practice*. ed 2, 2000, Saunders, Philadelphia, *Chapter that provides an excellent section on measurement and interpretation of CVP*.

S Haskins, PJ Pascoe, JE Ilkiw, et al.: Reference cardiopulmonary values in normal dogs. *Comp Med*. **55**, 2005, 156, *A reference that provides the first published normal values compiled from a large number of dogs that had pulmonary artery catheters placed and TDCO monitoring*.

M Mellema: Cardiac output, wedge pressure, and oxygen delivery. *Vet Clin North Am Small Anim Pract*. **31**, 2001, 1175, *A reference that provides an excellent review of cardiovascular parameters and the alterations that can occur with critical illness*.

MH Valtonen, LM Eriksson: The effect of cuff width on accuracy of indirect measurement of blood pressure in dogs. *Res Vet Sci*. **11**, 1970, 358, *Paper that compared the effects of varying cuff widths on blood pressure measurements obtained on dogs of varying sizes via an indirect blood pressure monitor*.

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[*] See the CD-ROM for a complete list of references

204 Chapter 204 Urine Output

Sean Smarick, VMD, DACVECC

204.1 KEY POINTS

- Measuring urine output assists the clinician in the assessment of perfusion, renal function, and fluid balance.
- An indwelling urinary catheter is justified for the accurate determination of urine output in critically ill patients.
- Normal urine output is approximately 1 ml/kg of body weight per hour, but the interpretation of the urine output value depends on the individual patient and clinical situation.
- Oliguric and polyuric states require prerenal, postrenal, and renal considerations, with meticulous attention to fluid therapy.
- Once perfusion and hydration are assessed as normal, urine output can guide fluid administration rates by balancing intake and output.

204.2 URINE OUTPUT AS A MONITORING TOOL

Urine output is dependent on a number of upstream physiologic processes. For there to be normal urine output, the patient must have adequate perfusion, fluid balance, and renal function. As such, a normal urine output supports the clinical picture of a stable patient. Abnormal values indicate a problem and alert the clinician to search for the cause and adjust the patient's therapy. Once the patient's perfusion and hydration are stabilized, urine output can guide fluid therapy to maintain fluid balance by matching input with output.[1] A number of conditions often encountered in emergent or critically ill patients warrant monitoring urine output on some level.

204.3 MEASUREMENT

Urine output is measured most accurately and easily by collecting urine from an indwelling urinary catheter. The catheter collects urine as it is produced and is indicated for monitoring perfusion and renal function in critically ill patients. The risk of a catheter-associated urinary tract infection can be minimized by placement and maintenance protocols that include aseptic technique and leaving the catheter in place for only as long as necessary[2] (see Chapter 138, Urinary Catheterization). Graduated cylinders or beakers should be used to measure urine volume because collection bag graduations are inaccurate.

When intensive monitoring of urine output is not necessary, “free catch” methods of collecting urine can be used. These include metabolic cages, collection pans, and absorbent pads. Metabolic cages are rarely used in the clinical setting, and collection pans provide an option for the ambulatory patient. Absorbent pads can be very effective as long as the patient voids the entire urine volume on the pad. Recumbent patients are good candidates for this method because they are forced to urinate in a given position. The absorbent pads are preweighed and then weighed again immediately after the patient urinates. Output is estimated by the change in weight assuming that 1 milliliter of urine weighs 1 gram.

In all hospitalized patients, especially those receiving fluid therapy, screening urine output with a gross estimation of the volume is indicated as part of the patient's ongoing assessment. Gross estimation may be adequate for basic monitoring of initial resuscitation, ongoing fluid therapy, and surveillance for obstruction in stable patients. However, more accurate measurements should be performed if the patient remains or becomes critically ill or if the adequacy of urine output is questioned.

204.4 DETERMINANTS

Urine output is dependent on the glomerular filtration rate (GFR), tubular reabsorption of solutes and water, and patency of the urinary tract. Ultrafiltration of plasma at the glomerulus is the first step in urine production, and any decrease in GFR will result in decreased urine output. The ultrafiltrate travels through the nephron, and tubular reabsorption generally leaves less than 1% of the original volume to be excreted as urine. If there is a physiologic or pathologic decrease in these reabsorptive processes, an increase in urine production will result, whereas an increase in tubular reabsorption of solutes and water will result in a decrease in urine output. Lastly, urine output depends on an unobstructed path from the kidney to the urethral opening.

204.4.1 Glomerular Filtration Rate

The GFR is determined by the balance of hydrostatic and colloid osmotic forces across the glomerular membrane in addition to the permeability and surface area of this membrane. Between mean arterial blood pressures of 80 and 180 mmHg, autoregulation maintains renal blood flow, and therefore GFR is constant. Patients with a mean arterial blood pressure below 80 mmHg will have decreased renal blood flow, GFR, and urine output. Furthermore, decreased baroreceptor stimulation, as occurs in response to hypotension and hypovolemia, will increase sympathetic input to the kidneys and circulating catecholamine and angiotensin production. These mediators cause renal arteriolar constriction, further decreasing renal blood flow and GFR in an effort to conserve blood volume.

204.4.2 Tubular Reabsorption of Water and Solutes

Although large volumes of plasma are filtered by the glomerulus, over 99% of the ultrafiltrate normally is 865
reabsorbed by active and passive mechanisms throughout the nephron. This assumes a critical mass of 866
functioning nephrons. The amount of ultrafiltrate that is excreted as urine is fine-tuned by a number of systems that regulate extracellular fluid volume and water balance.

Stretch receptors (baroreceptors) throughout the body are the primary regulators of effective circulating volume. Hypotension and hypovolemia cause decreased stretch, reducing the activity of these receptors and resulting in activation of the sympathetic nervous and renin-angiotensin-aldosterone systems. This response increases reabsorption of solutes and water in an effort to maintain the effective circulating volume, resulting in decreased urine output. The converse is also true. Increased vascular volume will decrease renal reabsorption of solutes and water and increase urine output by activation of atrial natriuretic peptide and decreased stimulation of the renin-angiotensin-aldosterone system.

Antidiuretic hormone (ADH) also influences urine output. It is released primarily in response to increased extracellular osmolality, but it will also be released in response to significant decreases in effective circulating volume. ADH increases the amount of water being reabsorbed in the distal nephron, decreasing urine output.

Dysfunctional nephrons, pharmacologic interference with the absorptive mechanisms, or pathologies of the fine-tuning systems can therefore affect urine output.

204.4.3 Impedance to Flow

As the ultrafiltrate leaves the collecting ducts as urine, it flows through the renal pelvis, into the ureter, the bladder, and finally out the urethra. Obstructions will prevent urine flow as well as transmit back pressure to the kidneys, resulting in decreased GFR and renal dysfunction of the affected kidneys.[1,3]

204.5 NORMAL URINE OUTPUT

Normal values for urine output have been reported for both adult dogs and cats and are generally accepted as 1 ml/kg of body weight per hour. Urine serves to excrete metabolic waste and if a patient is anorexic, deprived of food, caged, or in a sedentary state, output may be 0.5 ml/kg/hr or even lower. Conversely, neonates that lack effective urine concentrating abilities, or patients on fluid therapy at rates exceeding those needed to replenish deficits and meet maintenance requirements, may have urine output in excess of 2 ml/kg/hr. Interpretation of urine output depends on the individual patient and clinical situation.[1,3]

204.6 ABNORMAL URINE OUTPUT

Abnormal urine output alerts the clinician to consider prerenal, renal, and postrenal causes for the oliguric or polyuric state. As a downstream parameter, abnormal urine output is not specific for any one cause, and abnormal values warrant a complete rule-out list. For example, although decreased urine output may indicate inadequate resuscitation in a trauma patient in severe shock, it must be considered that oliguria can have other causes such as urinary tract trauma. Hence, other indicators of perfusion and urinary tract trauma must be examined to develop an accurate clinical picture.

204.6.1 Oliguria

A decrease in urine output below what is expected (the lowest normal value in dogs being reported as 0.27 ml/kg/hr) is referred to as *oliguria,* and the total lack of urine production is called *anuria.* [1] Oliguria warrants immediate concern and should prompt the clinician to differentiate between prerenal, renal, and postrenal causes. Prerenal and postrenal causes are ruled out first, followed by evaluation of intrinsic renal abnormalities. Fluid therapy may need to be increased or decreased depending on the cause, and other therapies may be indicated (see Chapter 71, Syndrome of Inappropriate Antidiuretic Hormone).

204.6.1.1 Prerenal Oliguria

Renal perfusion is necessary to maintain normal urine output. Inadequate renal perfusion will decrease GFR and increase tubular resorptive mechanisms as described above. Reduced cardiac output or hypotension causes decreased renal perfusion. Common disease processes associated with these changes include severe dehydration, hypovolemia, hemorrhage, cardiac failure, and the systemic inflammatory response syndrome and sepsis.

Restoring adequate circulating volume, cardiac function, and vascular tone should restore urine output to normal if poor perfusion is the sole cause of the oliguria.

Urine sodium concentration can also be measured to support the assessment of poor renal perfusion. A urine sodium level of less than 20 mEq/L is consistent with the action of aldosterone and supports the presence of inadequate renal perfusion (in the absence of diuretics or intrinsic renal disease).[4]

204.6.1.2 Postrenal Oliguria

A decrease in urine output always warrants an assessment of the patency of the urinary tract, including evaluation of the urinary catheter and closed collection system if one is in place. Obstruction or disruption of the urethra, bladder, or ureters generally will lead to oliguria or anuria. A large, inexpressible bladder on palpation warrants evaluation for a lower urinary tract obstruction due to calculus, tumor, clot, or foreign body. Increased bladder sphincter tone due to upper motor neuron disease or pharmacologic effects of drugs such as morphine should also be considered. Radiographs, abdominal ultrasonography, urinary catheterization with or without retrohydropulsion, or contrast cystourethrogram may be warranted to characterize the lesion. Urethrocystoscopy can also be considered for the evaluation of urethral disease.

Unilateral ureteral (or renal pelvic) obstruction or disruption may not result in decreased urine output because the other kidney may compensate. In these patients, urine output depends on the function of the remaining kidney, including the patency of its renal pelvis and ureter. Ureteral obstructions may be challenging to diagnose because “big kidney-little kidney” radiographs are not specific for the condition, and effective imaging with ultrasonography and contrast studies may require advanced training and equipment. If urinary tract obstruction cannot be relieved readily, fluid therapy must be adjusted to prevent volume overload.

204.6.1.3 Renal Oliguria

A critical mass of functioning nephrons is required to produce an adequate amount of urine. Intrinsic acute renal failure or end-stage chronic renal failure is characterized by a lack of functioning nephrons that simply does not allow enough urine to be made. Renal causes of oliguria are suspected when prerenal and postrenal causes have been ruled out. The history and other diagnostic tests, such as abdominal ultrasonography, may further support this diagnosis. When managing intrinsic renal disease, fluid therapy must be adjusted to prevent volume overload. Persistent oliguria or anuria is a poor prognostic indicator in veterinary medicine, especially in the absence of renal replacement therapy.[1] 866 867

The syndrome of inappropriate secretion of ADH is a potential cause of oliguria in critically ill patients. Causes include recent surgery, administration of μ-agonist narcotics, and positive-pressure ventilation. These animals have oliguria despite adequate renal perfusion and do not have evidence of renal or postrenal compromise. Serum hyponatremia is usually evident and if concurrent urine electrolytes are measured, a urine sodium level of greater than 40 mEq/L supports the diagnosis. Low-dose loop diuretics such as furosemide will usually maintain sufficient urine output until the stimulus is no longer present.[1,3,4]

204.6.2 Polyuria

Urine excretion greater than 1 to 2 ml/kg/hr represents polyuria. As with oliguria, prerenal, postrenal, or renal causes should be considered and therapy adjusted accordingly.

204.6.2.1

Prerenal Polyuria

Overhydration caused by administering fluids in excess of what is needed is a common cause of polyuria in the hospitalized patient. Fluid therapy may also result in medullary washout, leaving the kidney unable to concentrate urine. Primary hormonal alterations, electrolyte abnormalities, osmotic loads, and drugs can also affect the kidney's ability to absorb solute and water (Box 204-1). Careful attention to fluid therapy is required in the polyuric patient to prevent significant abnormalities in hydration. When polyuria occurs in response to excess fluid administration, it is an appropriate response that does not require additional fluid therapy.

204.6.2.1.1

Box 204-1 Prerenal Causes of Polyuria

204.6.2.1.1.1

Increased intake

Polydipsia (psychogenic)

Fluid administration

204.6.2.1.1.2

Drugs

Diuretics

α_2-Agonist sedatives

κ-Agonist narcotics

Alcohols

Glucocorticoids

Anticonvulsants

204.6.2.1.1.3

Hormonal conditions

Hyperadrenocorticism

Hypoadrenocorticism

Diabetes insipidus

Hyperthyroidism

Cerebral salt-wasting syndrome (after traumatic brain injury)

204.6.2.1.1.4

Electrolyte abnormalities

Hypokalemia

Hypercalcemia

204.6.2.1.1.5

Osmotic conditions

Diabetes mellitus

Salt ingestion or administration

Glycols

204.6.2.1.1.6

Others

Escherichia coli endotoxin

Liver disease

204.6.2.2

Postrenal Polyuria

Postobstructive diuresis is a common cause of polyuria often encountered in small animal patients after relief of a urinary tract obstruction. Proximal tubule dysfunction, altered ADH responsiveness, and osmotic diuresis contribute. Aggressive fluid administration is warranted to maintain fluid balance until renal function and solute load return to normal.[1,4]

204.6.2.3

Renal Polyuria

Chronic renal failure usually is characterized in small animals by a progressive loss of nephrons. As a result, the kidney can no longer fully reabsorb the filtered load of sodium and water and a polyuric state results. In polyuric renal failure, monitoring urine output assists in balancing fluid administration, and the clinician will quickly recognize deterioration into oliguric renal failure.[1] Conversely, patients recovering from acute renal failure will often progress from an oliguric state to one of polyuria.

204.7 FLUID BALANCE

Measuring urine output is a valuable tool in balancing fluid therapy in oliguric and polyuric states, or in patients that are critically ill and need tight control over their extracellular fluid volume. In homeostasis, there is no net loss or gain of water and solutes; the intake of fluids is equal to that excreted. The more of the output part of the equation that is known, the better the fluid plan one can develop. When calculating a patient's fluid output, both sensible and insensible losses must be considered. Sensible losses are those that can be measured, such as urine, whereas insensible losses are those that cannot be measured, such as evaporation. Evaporative losses are less than 20 ml/kg/day in sedentary, quiet dogs and cats; however, panting, active dogs can lose as much as 70 ml/kg/day.[1] Drooling and feces can be measured by weighing as described previously, but they often are considered insensible and negligible if normal in amount.

In patients with normal hydration status, a fluid plan based on matching intake and output is simple and effective. Essentially this fluid plan aims to measure all of the output over a specified period, such as 4 hours, and this volume is used to determine the new fluid administration rate. This approach can be particularly beneficial in the polyuric patient because excessive fluid loss can occur rapidly.[1,4]

Body weight, physical examination, hydration parameters (moistness of mucous membranes, skin turgor, eye position), perfusion parameters (mentation, mucous membrane color, capillary refill time, pulse quality, heart rate, and extremity temperature), packed cell volume, serum total protein level, urine specific gravity, blood pressure, central venous pressure, and lactate level are parameters that can help assess the hydration and perfusion status of the patient for both initial and ongoing fluid therapy.

204.8 CASE EXAMPLE

As an example, a 5-kg cat, after a lower urinary tract obstruction has been relieved, has had a urine output of 120 ml over the previous 4 hours. A 50-ml fluid bolus was given initially and the patient received 2 ml/kg/hr (10 ml/hr) of an isotonic intravenous fluid for the 4-hour period. The patient's intake over the last 4 hours is 90 ml (50-ml bolus + [4 hr × 5 kg × 2 ml/kg/hr]) and the patient's output was 120 ml, a deficit of 30 ml. After determining that the patient currently is appropriately perfused and hydrated, the diagnosis of postobstructive diuresis is made. To balance the intake and output, the fluid rate would be increased to replace the 30-ml deficit over the next 4 hours (to a total of 17.5 ml/hr). Once the fluid rate is approximately equal to the urine output, it is decreased gradually to a maintenance rate; the urine output should follow.

If this same patient generated only 4 ml of urine during the first 4 hours (0.2 ml/kg/hr), inadequate resuscitation, catheter or urinary tract obstruction, or acute renal failure should be considered. If there are signs of inadequate perfusion or dehydration, additional fluids should be administered as appropriate. Integrity and patency of the urinary tract is assessed by palpation of the bladder and flushing the catheter, and if there is still a question of an intact lower urinary tract, imaging studies are performed. Lastly, if no evidence to support prerenal or postrenal causes of oliguria is found, then acute renal failure is considered.

204.9 SUGGESTED FURTHER READING*

S DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 3, 2006, Saunders, St Louis, *A well-written and referenced textbook that provides both practical and academic information on* *everything germane to fluid therapy, including an excellent overview chapter on renal physiology. A must-have reference for any small animal practitioner.*

SD Smarick, SC Haskins, J Aldrich, et al.: Incidence of catheter-associated urinary tract infection among dogs in a small animal intensive care unit. *J Am Vet Med Assoc*. **224**, 2004, 1936, *A prospective study of catheter-associated urinary tract infections demonstrating a low incidence in urinary catheters placed to monitor urine output in critically ill dogs.*

* See the CD-ROM for a complete list of references

205 Chapter 205 Colloid Osmotic Pressure And Osmolality

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205.1 KEY POINTS

- Determination of colloid osmotic pressure (COP) can guide artificial colloid therapy in veterinary patients.
- Estimation of COP via equations using the patient's albumin and globulin concentrations are unreliable, particularly in critically ill patients that may have altered albumin-to-globulin ratios.
- Direct measurement via a colloid osmometer is the only reliable way to monitor COP.
- Maintenance of a goal COP of at least 15 mm Hg in whole blood for both dogs and cats reduces the risk of edema formation and secondary organ dysfunction associated with edema.
- Plasma osmolality can be estimated from an equation or measured directly via a freezing point depression osmometer.
- Diagnosis of an osmolal gap (measured plasma osmolality – estimated plasma osmolality) of greater than 10 mOsm/kg indicates the presence of another osmolal, such as ethanol or ethylene glycol and its metabolites, and may be clinically useful in diagnosing these toxicities.

205.2 INTRODUCTION

Colloid osmotic pressure (COP) is the physiochemical phenomenon that occurs when two solutions with different colloid concentrations are separated by a semipermeable membrane. The particles contributing to COP (and the particles that they may hold with them because of their electrical charge) do not pass readily through the semipermeable membrane. This is in contrast to most crystalloid particles such as electrolytes, glucose, and other metabolites, which pass readily through the membrane. COP is determined with a patient's blood sample in reference to normal saline rather than pure water because normal saline is more representative of the fluid in the interstitial space. COP should be thought of as the osmotic pressure exerted by plasma proteins and their associated electrolytes, because the electrolytes contribute significantly to the COP.

Albumin and its associated cations provide approximately 60% to 70% of the plasma oncotic pressure and globulins provide the remaining 30% to 40%. Oncotic pressure is defined as the osmotic pressure exerted by colloids in solution, so the terms *COP* and *oncotic pressure* can be used interchangeably; colloid oncotic pressure, a commonly used misnomer, is redundant.

Osmolality is the concentration of osmotically active particles (solute) per kilogram of solution. The size and charge of the particles does not matter when determining the osmolality; only the number of particles in solution is relevant.

205.3 COLLOID OSMOTIC PRESSURE

205.3.1 Starling Hypothesis

The Starling hypothesis states that fluid flux at the capillary level is controlled by a balance between hydrostatic pressure and osmotic pressure gradients between the capillaries and interstitial space.

$$J_v = K_{fc}([P_c - P_i] - \sigma[\pi_p - \pi_i])$$

J_v = Net rate of capillary filtration

K_{fc} = Capillary filtration coefficient

P_c = Capillary hydrostatic pressure

P_i = Interstitial hydrostatic pressure

σ = Osmotic reflection coefficient

π_p = Plasma oncotic pressure

π_i = Interstitial oncotic pressure

This equation shows the importance of plasma COP in maintaining a normal fluid balance between the intravascular space and the interstitial space (Figure 205-1). If the COP in the capillaries drops lower than the COP in the interstitium, fluid will move out of the vessels and edema formation will be favored.

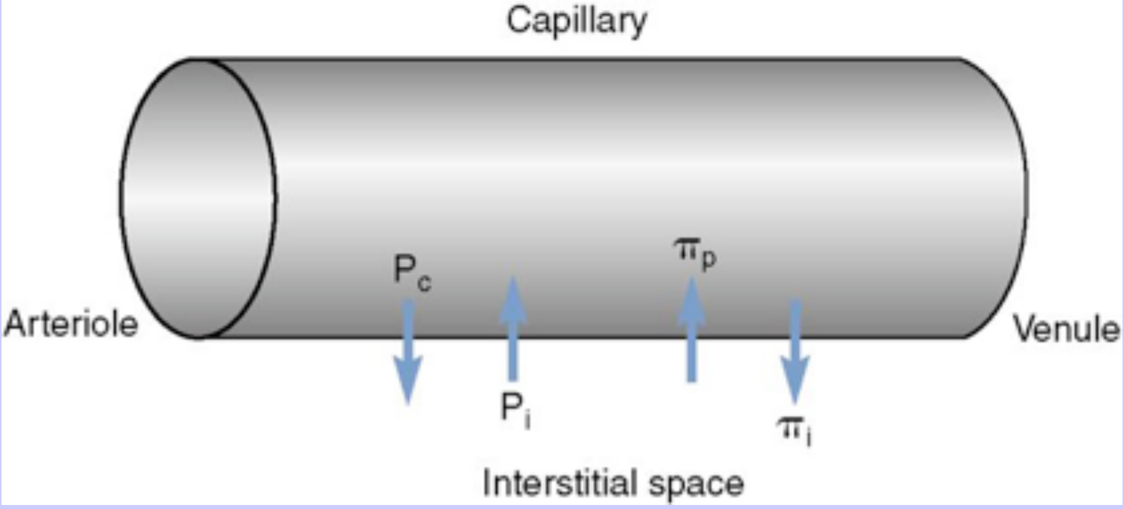
Of all the variables included in this equation, we can clinically manipulate only the COP and the capillary hydrostatic pressure. Increasing capillary hydrostatic pressure by administering intravenous fluids will tend to increase edema formation. By measuring COP in the blood and tapering the patient's fluid therapy toward maintaining a normal COP, we can try to prevent transvascular fluid efflux and the clinical problems associated with it, including interstitial edema and cavitary effusions.

205.3.2 Calculated Versus Measured Values

Equations have been developed to try to predict COP. For humans, the Landis-Pappenheimer equation can be used where P = plasma protein, and:

$$COP = 2.1\,P + 0.16P^2 + 0.009P^3$$

Figure 205-1 Starling hypothesis of fluid flux across the capillary membrane, where P_c = capillary hydrostatic pressure, P_i = interstitial hydrostatic pressure, π_p = plasma oncotic pressure, and π_i = interstitial oncotic pressure.



This equation is unreliable in other species, including cats, dogs, cattle, and horses, because they have different albumin-to-globulin ratios. Species-specific equations have been derived[1] but are not reliable in critically ill patients whose protein concentrations (specifically the albumin-to-globulin ratio) may be altered.[2]

Unfortunately, these equations do not provide an alternative for direct measurement of COP because of the changes associated with illness. Although total solids certainly give an indication of hypoproteinemia and therefore a low COP, refractometry cannot accurately predict COP. Furthermore, once artificial colloids have been administered, the measurement of total solids via refractometry will be inaccurate. Most artificial colloids have a refractometry reading of 4 to 4.5 mg/dl, so the patient's total solids level will appear to approach this range, even if it is actually lower. The only way to predict COP accurately, particularly in critically ill patients and those receiving artificial colloids, is a direct measurement via a colloid osmometer (Model 4420, Wescor, Logan, UT).

205.3.3 Normal Colloid Osmotic Pressure Values

Normal values for COP are species, sample, and laboratory dependent. Published normals for plasma are 23 to 25 mm Hg for cats and 21 to 25 mm Hg for dogs.[3] For whole blood, normal values are 24.7 ± 3.7 mm Hg for cats and 19.95 ± 2.1 for dogs.[4] When using whole blood for COP measurement, samples should be collected with lyophilized heparin, which is commonly available in green-top tubes. Slight variability does occur from one laboratory to another, so normal values should be established for each setting.

Samples of plasma or serum that cannot be processed immediately may be frozen and later thawed for determination of COP, with little effect on the accuracy of the values obtained. Whole blood samples can be refrigerated and processed within 24 hours without any significant effect on the COP. Care should be taken to prevent hemolysis of the sample, because free hemoglobin can increase COP. Dilution of the COP from anticoagulants can occur, which is why lyophilized heparin is preferred. It is provided in a dry form, has a high molecular weight, and is used in a very low concentration, so it will have a minimal effect on COP.

205.3.4 Colloid Osmotic Pressure in Critically Ill Patients

COP has been measured in whole blood in 124 critically ill cats and dogs. Mean values obtained were 13.9 ± 3.1 mm Hg (range 7.6 to 23.8).[5] The normal values for this laboratory were as listed above for whole blood. Critically ill cats and dogs can have substantial decreases in their COP values and can benefit greatly from COP monitoring and therapy aimed at correcting a low COP.

205.3.5 How Colloid Osmotic Pressure Is Measured

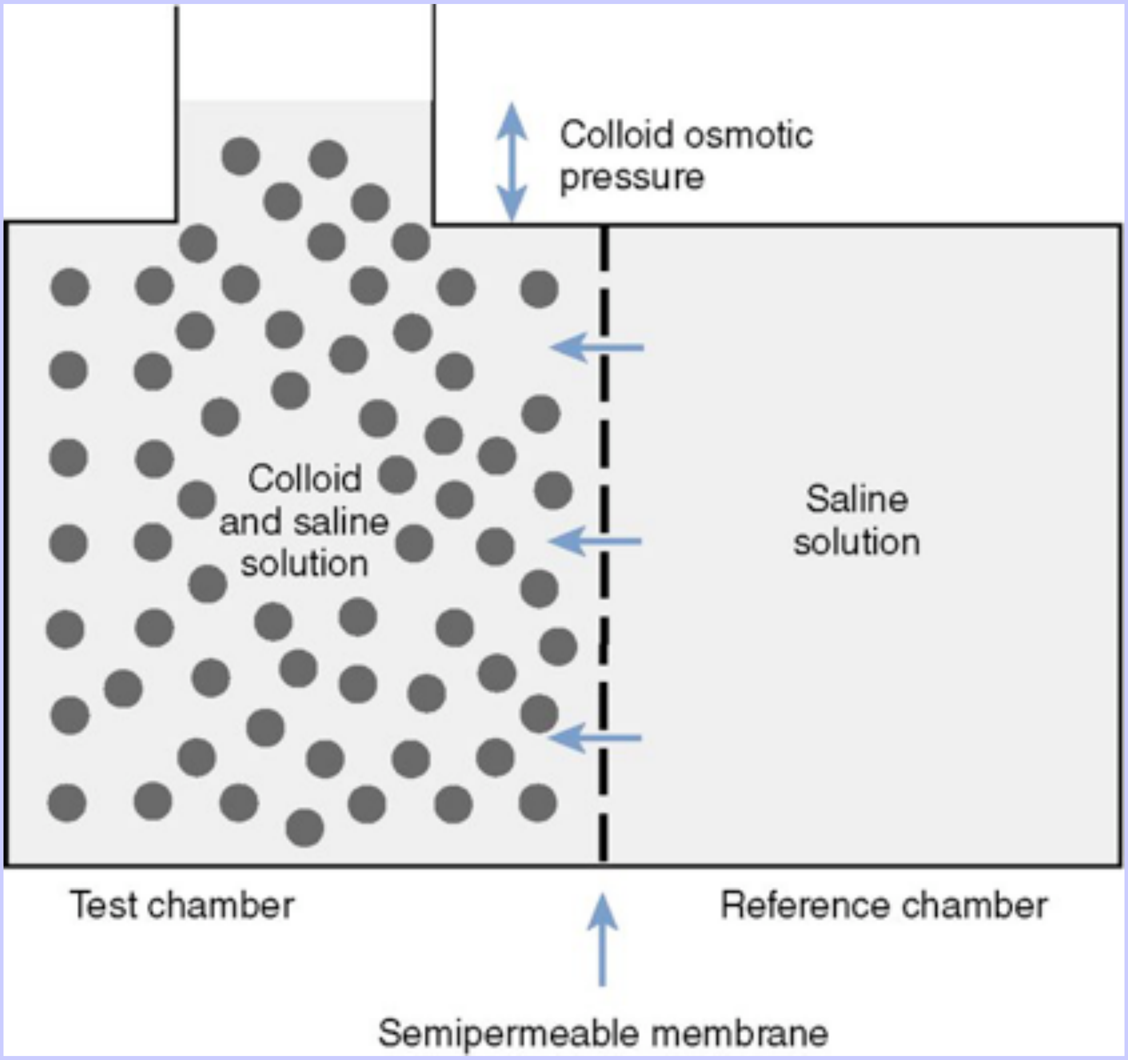
The colloid osmometer determines the COP of a solution using a semipermeable membrane. The membrane has a uniform pore size that allows only molecules with a MW of less than or equal to 30,000 daltons to pass 869 through, simulating the capillary endothelium in veterinary patients. This membrane separates 870 two chambers, a reference chamber filled with 0.9% saline and a test chamber where the patient sample is injected. The sample can be serum, plasma, or whole blood (normal ranges will vary slightly depending on which is used).

The membrane is relatively impermeable to the proteins because of their large size. Water will migrate from the reference chamber into the test chamber as a result of differences in the colloid concentration and COP (Figure 205-2). The COP as determined by the membrane is not only dependent on the colloid concentration, but also the Gibbs-Donnan effect, which takes into account the negative charge of the proteins. Electroneutrality must be maintained on each side of the membrane. The negative charge of the proteins causes retention of positively charged ions, which increases the concentration of these normally diffusible ions in the test chamber.

Because osmotic pressure is proportional to the number of molecules present, not the size of the molecules, the cations contribute significantly to the COP. The actual contribution of these ions to the COP can be determined by the square of the electrical charge carried by the colloid component. Because the total measured COP is determined by both the colloid and the associated positive anions, the COP is related nonlinearly to the colloid concentration. The charge of the proteins in a sample depends on the pH of the sample and the electrophoretic pattern of the proteins. These may be very abnormal in critically ill patients, making direct measurement of the COP all the more essential.

After equilibrium has been established between the two chambers (within 30 to 90 seconds), a negative pressure gradient exists in the reference chamber. A sensing diaphragm next to the fluid in the reference chamber is attached to a pressure transducer. Minute pressure changes in the reference chamber are converted into alterations in electrical impedance, which is measured, amplified, then converted into a display on the osmometer that is reported in mmHg.

Figure 205-2 Measurement of colloid osmotic pressure in a colloid osmometer across a semipermeable membrane. The colloid in the patient's sample, placed in the test chamber, cannot move across the semipermeable membrane. This draws water across the membrane from the reference chamber. The difference in pressure is measured as the colloid osmotic pressure.



205.3.6 Indications for Colloid Osmotic Pressure Measurement

COP measurement should be part of routine monitoring in any patient receiving artificial colloids, in patients with edema, and in patients that are treated with aggressive crystalloid therapy or have low serum albumin concentration. Monitoring of COP can hopefully prevent edema formation in the latter two groups of patients by allowing the clinician to direct therapy toward correcting a low COP. Fortunately, COP measurement requires a very small sample of blood or serum, less than 0.5 ml. COP may need to be measured daily or more frequently in patients receiving large amounts of crystalloid or colloid fluid therapy, because it can change rapidly, particularly if boluses are given.

Edema of organs such as the heart, causing increased ventricular stiffness and decreased end-diastolic volume, stroke volume, and cardiac output, and lungs, causing interstitial edema and increased work of breathing, can lead to multiple organ dysfunction long before clinically appreciable peripheral edema is present. By correcting low COP in critically ill patients, some of these secondary problems that contribute to patient morbidity and mortality can hopefully be prevented.

A low COP in a critically ill patient can and should be managed with plasma, human albumin solutions, or artificial colloids such as hydroxyethyl starch or dextran. In human patients, lower COP has been associated with decreased survival, particularly before the use of artificial colloids became commonplace.[6] In a more recent study, COP was not significantly different between survivors and nonsurvivors in patients with a critical illness of at least 7 days duration. In this study, however, artificial colloids could be used as directed by the patients' physicians, and mean COP in all patients was 16.1 mmHg.[7] This maintained the COP value above the cutoff that had previously been associated with increased mortality. It could be argued that by managing a patient's low COP with artificial colloids and albumin, this risk factor is eliminated in critically ill patients, and therefore the overall chance of survival is improved.

205.4 OSMOLALITY

205.4.1 Definition

Osmolality is the number of particles of solute per kilogram of solvent, and osmolarity is the number of particles of solute per liter of solvent. Both are purely dependent on the number of particles in solution; the particle size, shape, density, or electrical charge has no relevance. In body fluids, they are almost exactly equal because the solvent is primarily water, and 1 kg water = 1 L water. Normal values for osmolality in dogs are 290 to 310 mOsm/kg and in cats 290 to 330 mOsm/kg.[8]

205.4.2 Determination of Osmolality

Plasma osmolality can be estimated by using the following equation:

Calculated plasma osmolality $= 2\,\mathrm{Na}^{+}\,(\mathrm{BUN} \div 2.8) + (\mathrm{glucose} \div 18)$ where BUN = blood urea nitrogen and Na^{+} = sodium.

Sodium concentration is multiplied by a factor of 2 to include the chloride and bicarbonate that are present to maintain electroneutrality. Concentrations of urea and glucose are measured in mg/dl and must be converted to 870
millimoles per liter by the conversion factor of 2.8 for BUN and 18 for glucose. Common causes of increased 871
calculated plasma osmolality include hypernatremia, hyperglycemia secondary to diabetes mellitus, and azotemia (Box 205-1; see section below, Effective Osmolality). The most common cause of a decreased calculated plasma osmolality is hyponatremia (see Chapters 54, 67, and 68, Sodium Disorders, Diabetic Ketoacidosis, and Hyperglycemic Hyperosmolar Syndrome, respectively).

205.4.2.1 Box 205-1 Common Causes of Hyperosmolality in Small Animals

205.4.2.1.1 Effective Osmoles

- Sodium
- Glucose
- Mannitol
- Ketoacids
- Lactic acid
- Phosphates and sulfates (with renal failure)
- Radiopaque contrast solutions

205.4.2.1.2 Ineffective Osmoles

- Blood urea nitrogen
- Ethylene glycol and metabolites
- Ethanol and methanol
- Acetylsalicylic acid
- Isopropyl alcohol

Actual measurement of serum osmolality can be determined indirectly by using a freezing-point depression osmometer (most commonly) or determining the vapor point depression of the solution. For every 1 mole of nondissociating molecules dissolved in 1 kg (or 1 L) of water, the freezing point depression is decreased by 1.86° C. The osmolality of this solution would be 1 Osm/kg or 1000 mOsm/kg.

205.4.3 Osmolal Gap

The difference between the measured and calculated serum osmolality is referred to as the *osmolal gap*. The measured value should not be more than 10 mOsm/kg higher than the calculated plasma value.[9] If it is, this indicates the presence of an unmeasured solute that is present in a large amount in the plasma. This could be due to any solute that is not accounted for in the equation, and can include lactic acid, sulfates, phosphates, acetylsalicylic acid, mannitol, ethylene glycol and its metabolites, ethanol, isopropyl alcohol, methanol, radiographic contrast solution, paraldehyde, sorbitol, glycerol, propylene glycol, or acetone (see Box 205-1).[9,10]

It has been reported that commercially available activated charcoal suspensions that contain propylene glycol or glycerol can cause an increased serum osmolality in healthy dogs.[10] This may result in difficulty interpreting serum osmolality when evaluating for some toxins (such as ethylene glycol) if activated charcoal is administered before obtaining blood samples for measurement of serum osmolality. An increased osmolal gap can also occur with pseudohyponatremia secondary to hyperlipidemia, marked hyperglycemia, or hyperproteinemia.[8,9] Newer methods of measuring plasma electrolytes with ion-selective electrodes has helped to circumvent this problem.

205.4.4 Effective Osmolality

Because some molecules such as urea are freely diffusible across cell membranes, changes in their concentrations do not cause fluid shifting between the intracellular and extracellular compartments. Other molecules, most importantly sodium but also glucose, chloride, and others, do not readily cross cell membranes, and therefore will cause water movement. Effective osmolality, also known as *tonicity,* can be estimated as:

$$\text{Calculated effective osmolality} = 2\,\text{Na}^{+} + (\text{glucose} \div 18)$$

This is the same as the previous equation for calculated plasma osmolality without BUN, which is an ineffective osmole. This can become important when evaluating azotemic patients. If they have a high BUN, the calculated osmolality will be increased, but their effective osmolality or tonicity may be normal or decreased. Direct measurement of freezing point depression osmolality cannot distinguish between effective and ineffective osmoles.[6]

Evaluation of osmolality, both calculated and measured, can be important for recognition and treatment of several clinical conditions including sodium disorders, hyperglycemia, and certain toxicities (see Box 205-1). Therapy will be aimed at preventing rapid changes in osmolality because adverse reactions, especially neurologic, may result if the serum osmolality is changed abruptly.

205.4.5 Urine Osmolality

Urine osmolality can be used to assess the concentrating ability of the kidney. Interpretation of urine osmolality requires knowledge of the hydration and intravascular volume status of the patient. This will allow for differentiation of an appropriate versus abnormal physiologic response of the kidneys. The urine osmolality is useful for differentiating sodium disorders, identifying the syndrome of inappropriate antidiuretic hormone (see Chapter 71, Syndrome of Inappropriate Antidiuretic Hormone), differentiating prerenal from renal causes of azotemia, and diagnosing diabetes insipidus.

205.5 SUGGESTED FURTHER READING*

SA Brown, K Dusza, J Boehmer: Comparison of measured and calculated values for colloid osmotic pressure in hospitalized animals. *Am J Vet Res*. **55**, 1994, 910, *Paper about a study that measured and calculated COP in normal and hospitalized canine, feline, and bovine patients, with calculated values determined using* *protein concentrations from refractometer readings or actual measurements of albumin and globulin; closest correlation found in healthy animals with measured albumin and globulin*.

SP DiBartola: Disorders of sodium and water. In SP DiBartola (Ed.): *Fluid, electrolyte and acid-base disorders in small animal practice*. ed 3, 2006, Saunders, Philadelphia, *A book chapter that contains an excellent review of osmolality, osmolal gap, and effective osmolality*.

BF Feldman, DP Rosenberg: Clinical use of anion gap and osmolal gap in veterinary medicine. *J Am Vet Med Assoc*. **178**, 1981, 396, *One of the original papers that described the use of osmolal gap in clinical veterinary patients*.

E Rudloff, R Kirby: Colloid osmometry. *Clin Tech Small Anim Pract*. **15**, 2000, 119, *A good review of colloid osmometry in canine and feline patients and includes the published normal measured COP values for plasma in these species. Also includes clinical case examples to show how COP measurement can guide fluid therapy*.

MH Weil, RJ Henning, VK Puri: Colloid oncotic pressure: Clinical significance. *Crit Care Med*. **7**, 1979, 113, *Paper that reviewed the human literature at the time and presented data from a number of studies that evaluated COP and risk of pulmonary edema formation, rate of clearance of pulmonary edema, and mortality*.

* See the CD-ROM for a complete list of references

206 Chapter 206 Intraabdominal Pressure

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206.1 KEY POINTS

- Intraabdominal hypertension affects every organ system of the body and can predispose to multiple organ dysfunction and failure.
- Intraabdominal pressure (IAP) can be dangerously elevated in disease states that do not primarily involve the abdomen.
- Measurement of IAP is minimally invasive and simple.
- Trends are more useful than a single measurement in helping to assess organ perfusion and assist in decision making.

206.2 INTRODUCTION

Intraabdominal pressure (IAP) and intraabdominal hypertension (IAH) have been recognized in animals and humans for over 150 years.[1,2] A discussion of IAP in pregnancy was published in 1913, and the effects of IAH on renal function in people was described in 1947.[3,4] One of the first published studies was undertaken simply to prove whether IAP was positive or negative and involved a series of very different procedures in different species.[1] Original research into the physiologic effects of IAH was performed in several species once the normal IAP was established.[2] These studies were quite variable, not often repeated, and used techniques that we would find unacceptable for technical and humane reasons today. Scientists believed it was important to establish the parameters at that time, though, as surgery and interventional medicine was evolving.

IAP refers simply to the pressure within the abdominal cavity, regardless of the actual reading. IAH refers to increased IAP (>5 cm H_2O) in a general way, with or without abdominal compartment syndrome (ACS). ACS occurs when the IAH is causing adverse effects on physiologic function, usually at or near 35 cm H_2O. It is considered primary ACS if the trauma or disease occurs within the abdominal cavity (fractured liver or spleen, penetrating foreign body, peritonitis, neoplasia, hepatic abscess, pancreatitis) or secondary if the inciting disease is extraperitoneal (burns or thoracic trauma, usually followed by massive fluid resuscitation or high-pressure mechanical ventilation).

Both primary and secondary ACS are associated with multiple organ dysfunction and a worsened prognosis.[5] This is an important distinction because it is highly recommended to monitor IAP in patients who do not have intraperitoneal disease. Resolution of the ACS can significantly improve outcome in patients without primary abdominal disease who develop multiple organ dysfunction.[6,7]

The effects of rising IAP on organ function are well documented.[8-11] Visceral perfusion, abdominal blood flow, central venous pressure, pulmonary pressures, cardiac output, and renal function are all adversely affected by an increasing IAP, and early changes can be seen when levels exceed 10 cm H_2O. Much of the research documenting systemic effects of ACS has been performed in dogs.[11-17] Little clinical work in veterinary medicine has documented the effects of ACS in hospitalized patients, however the disease processes in which it is recognized in humans exist in our small animal patients and the technology for monitoring and responding to changes are the same. Several comprehensive reviews of the subject have been published in the human medical literature.[18-21]

IAH has been documented in human patients with ruptured abdominal aortic aneurysm, abdominal hemorrhage from trauma, occluded mesenteric artery, ruptured or necrotic bowel, bile peritonitis,[10] blunt trauma to any of the abdominal organs, gastric perforations, bladder ruptures,[18] and large abdominal masses.[22] In many of these cases, there was a previous surgical procedure and the IAH mandated a reexploration of the abdomen. Fluid infusions and effusions in dogs,[11] morbid obesity,[23] antishock trousers,[24] and pregnancy in humans[3] are also conditions that have been documented to increase IAP.

206.3 METHODS OF INTRAABDOMINAL PRESSURE MEASUREMENT

IAP has been measured via catheters placed in the inferior vena cava, stomach,[25,26] urinary bladder, and the peritoneal cavity.[27] The urinary bladder method is the easiest to use in small animal patients and provides consistent, accurate measurements.[27] A urethral catheter is inserted aseptically so that the tip is just inside the trigone of the urinary bladder. A Foley catheter is preferred to ensure that the fenestrations lie just inside the bladder. A sterile urine collection system is attached in the usual way, but two three-way stopcocks are placed in the system. A water manometer is attached to the upright stopcock port. A 35-cc to 60-cc syringe of 0.9% sodium chloride or a bag of 0.9% sodium chloride and an intravenous administration set are attached to the distal stopcock port for filling the manometer and infusing the bladder. The bladder is emptied and 0.5 to 1 ml/kg of 0.9% sodium chloride is instilled to distend it slightly. This lessens the likelihood that the bladder wall will obstruct the catheter fenestrations.

The bladder is essentially a passive conduit of the pressure within the abdomen, although infusion of too much saline into it will falsely elevate the IAP. The system is zeroed to the patient's midline at the symphysis pubis and the manometer filled with isotonic saline. The stopcock is closed to the fluid source, so that the meniscus in the manometer can drop and equilibrate with the pressure in the urinary bladder. The difference between the reading at the meniscus and the zero point is the IAP. The patient should be laterally recumbent when obtaining measurements. Patient position affects measurement[28] and should therefore be the same at each measurement.

Appropriate aseptic technique for placement and handling of the urethral catheter and the measurement system prevents a urinary tract infection in an otherwise healthy dog.[29]

Normal IAP in dogs is 0 to 5 cm H_2O. Healthy dogs undergoing elective abdominal surgery (ovariohysterectomy) had a postoperative IAP ranging from 0 to 15 cm H_2O. No problems associated with IAH were observed.[29] Normal IAP has not been documented in cats. Clinically, the author has used the parameters noted for dogs when caring for cats, with good results.

206.4 PHYSIOLOGIC EFFECTS OF INTRAABDOMINAL HYPERTENSION

206.4.1 Hemodynamic Effects

Increases in IAP lead to elevations in central venous pressure, pulmonary artery pressure, right atrial pressure, pulmonary capillary wedge pressure, mean arterial pressure, and systemic vascular resistance.[11,30,31] These changes are believed to develop in part because of catecholamine release and a subsequent shift of abdominal vascular volume into the thorax.[30]

Cardiac output may increase transiently with the initial increase in preload resulting from the vascular volume shift. Cardiac output then declines because venous return from the caudal part of the body is reduced and systemic vascular resistance is increased as a result of compression of the abdominal vasculature.[15,16] When graded increases in IAP were tested in dogs and pigs, urine output decreased,[4,17] and arterial and venous lactate levels increased.[14] These effects are largely due to the reduction in cardiac output. Increasing vascular volume with intravenous fluid infusions improved the reduced cardiac output associated with IAH. Surgical decompression improved oxygenation, cardiac output, and atrial filling pressures within 15 minutes in human patients.[9]

206.4.2

Renal Effects

Glomerular filtration rate and urine output were reduced in dogs with an IAP of 10 to 20 cm H_2O. Oliguria and anuria developed in these dogs with moderate to severe IAH of 25 cm H_2O or greater. The evidence suggests that this occurs because of reduced cardiac output and compression of the renal vasculature and parenchyma rather than a postrenal effect of pressure on the ureters.[17] Azotemia develops secondary to decreased blood urea nitrogen and creatinine excretion. Patients with ACS consistently experience improved urine output and a reduction in azotemia very quickly after surgical decompression.[4,9,17,29,32]

206.4.3

Pulmonary and Thoracic Effects

Pulmonary compliance is reduced with IAH.[28,33] Greater pressure on the peritoneal side of the diaphragm impairs its ability to contract and generate adequate subatmospheric intrathoracic pressure.[34] In mechanically ventilated pigs the negative hemodynamic effects of positive end-expiratory pressure combined with IAH led to a significant increase in blood lactate levels, as well as markedly increased central venous pressure, pulmonary capillary wedge pressure, and pulmonary artery pressure.[14,35] IAP monitoring is a valuable tool in assessing the numerous factors contributing to changes in pulmonary and hemodynamic function. Patients on mechanical ventilators with concurrent abdominal disease may benefit from having IAP measured. When pulmonary or cardiovascular parameters deteriorate, if IAH can be ruled out as a cause, the clinician's focus can be better directed to the true cause of deterioration. It has been suggested that elevated positive end-expiratory and peak inspiratory pressures may be the cause, rather than effect, of ACS. Regardless, both should improve with timely intervention when IAP exceeds 25 to 35 cm H_2O.[7]

206.4.4

Central Nervous System Effects

Intracranial pressure is increased with IAH.[23,35] Pressure is transmitted from the abdomen to the thorax. Increased thoracic pressures and blood volume in the more compliant compartments reduce venous blood flow in the jugular system and, therefore, drainage from the head.[34] This has been implicated in the central nervous system abnormalities associated with the morbidly obese as well as with iatrogenic pneumoperitoneum during laparoscopic procedures.[36] Signs of increasing intracranial pressure should be monitored carefully in patients with IAH. These include obtundation, changes in and loss of cranial nerve reflexes, vomiting, and seizures.

206.4.5 Visceral Effects

Hepatic, portal, intestinal, and gastric blood flow declined with an associated tissue acidosis in pigs with IAH.[37-39] Blood flow to the rectus sheath muscles is reduced with IAH, and this may impair wound healing.[40] Bowel tissue oxygenation is reduced as measured at the terminal ileum.[41] Bacterial translocation to the mesenteric lymph nodes in association with reduced blood flow in ACS at pressures of 34 cm H_2O has been documented.[42] Bacterial translocation predisposes the patient to sepsis and its sequelae (i.e., systemic inflammatory response syndrome and multiple organ dysfunction syndrome).[43]

206.4.6 Hormonal Effects

Several hormonal changes have been documented with IAH. An increase in plasma antidiuretic hormone occurred in dogs with externally applied abdominal pressures higher than 108 cm H_2O. This was prevented by a prior intravenous infusion of 6% dextran at 8 to 10 ml/kg.[13] Pigs had elevated plasma renin activity and aldosterone levels in response to IAH of 34 cm H_2O.[30] Decompression reversed the hormonal changes. In a pneumoperitoneum model, pigs had elevated levels of epinephrine and norepinephrine at an IAP of 27.2 cm H_2O but not 13.6 cm H_2O.[44] This study did not measure hormone levels after decompression. These changes probably relate to reduced renal perfusion and the baroreceptor and renin-angiotensin responses to a perceived reduction in blood pressure or volume.

206.5 GENERAL CONSIDERATIONS

As a general rule, the following pressure guidelines can be used to assist in clinical decision making in response to elevations in IAP (Table 206-1):

- If IAP is 10 to 20 cm H_2O, ensure that the patient is normovolemic and continue to pursue the underlying disease.

- If IAP is 20 to 35 cm H_2O, volume resuscitation may be necessary, diagnostic modalities to identify the cause should be instituted, and decompression should be considered.

Table 206-1 Interpretation of Intraabdominal Pressure and Recommendations for Therapy

IAP (cm H_2O)	Assessment	Recommended Action
5-10	Normal	No action, monitor.
10-20	Mild elevation	Ensure that the patient is normovolemic and continue to pursue the underlying disease.
20-35	Moderate to severe IAH	Volume resuscitation may be necessary, diagnostics to identify the cause should be instituted, and decompression should be considered.
>35	Severe IAH	Decompression is necessary to reverse organ damage and prevent further deterioration. Either paracentesis or surgical exploration is strongly recommended.

IAH, Intraabdominal hypertension; *IAP,* intraabdominal pressure.

- If IAP is greater than 35 cm H_2O, decompression either by paracentesis or surgical exploration is strongly recommended.

Obviously the breadth of physiologic changes associated with IAH makes the condition a concern in any patient with multisystem disease. Patients with traumatic damage to more than one body cavity often have significant muscle and organ trauma. These patients would benefit from IAP monitoring because bowel ileus, organ ischemia, progressive abdominal hemorrhage, or other problems that are not readily apparent clinically may develop. Dogs with acute, severe pancreatitis can develop effusions and infections that could cause IAH and a rapid deterioration of their clinical status.

IAP measurement provides another objective parameter to use in deciding if and when to perform a surgical exploration. Patients who have had major abdominal surgery may benefit from IAP measurement as a means of early identification of the need for follow-up procedures. For instance, increasing IAP in postoperative patients may indicate dehiscence of surgery sites or peritonitis from any source. If IAP is increasing and urine output is decreasing in spite of adequate fluid therapy, surgical intervention or paracentesis is indicated.[8,9,45] IAP changes can aid in the assessment of the need for paracentesis in patients with severe ascites. Procedures such as therapeutic or diagnostic peritoneal lavage and peritoneal dialysis may be better managed if IAP is monitored in conjunction with urine output and patient comfort.

Other situations that can lead to IAH, ACS, and organ dysfunction include intraperitoneal therapies and diagnostic tests. Iatrogenic IAH is generated during diagnostic peritoneal lavage, drug infusions such as intracavitary analgesics and antineoplastic agents, and peritoneal dialysis. Patient discomfort and negative effects can be linked to the increased IAP associated with those procedures.[46-48] The long-term effects are unknown, and there is some speculation that the length of time of IAH could affect the degree of impairment and improvement with decompression.[7] Short-term effects from iatrogenic IAH are more directly associated with patient comfort and quality of life.[46]

IAP is a valuable parameter to monitor in critically ill patients. Regardless of the presence of primary abdominal disease, IAP may rise in response to interventions and treatments and can ultimately result in multiple organ dysfunction and death. Controlled studies still need to be performed in the veterinary clinical setting to better assess those patients that will benefit most from its use and to establish more specific guidelines for action.

206.6 SUGGESTED FURTHER READING*

GL Bloomfield, PC Ridings, et al.: Effects of intra-abdominal pressure upon intracranial and cerebral perfusion pressure before and after volume expansion. *J Trauma*. **6**, 1996, 936, *A laboratory study in swine looking at the effects of IAP on intracranial pressure and changes with volume expansion*.

MC Chang, PR Miller, et al.: Effects of abdominal decompression on cardiopulmonary function and visceral perfusion in patients with intra-abdominal hypertension. *J Trauma*. **44**(3), 1998, 440, *A clinical study to characterize acute changes in visceral perfusion with IAH*.

MG Conzemius, JL Sammarco, DE Holt, DK Smith: Clinical determination of preoperative and postoperative intra-abdominal pressures in dogs. *Vet Surg*. **24**, 1995, 195, *The first clinical veterinary study to look at IAP in dogs before and after elective surgical procedures*.

T Kopelman, C Harris, R Miller, et al.: Abdominal compartment syndrome in patients with isolated extra-peritoneal injuries. *J Trauma*. **49**(4), 2000, 744–749, *A case series of patients with extraperitoneal disease who have developed ACS*.

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* See the CD-ROM for a complete list of references

207 Chapter 207 Capnography

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207.1 KEY POINTS

- Capnography allows the continuous, noninvasive assessment of partial pressure of arterial carbon dioxide.
- The normal gradient between end-tidal and arterial partial pressure of carbon dioxide (PCO_2) is less than 5 mmHg in small animal species.
- An increased end-tidal-to-arterial PCO_2 gradient indicates increased alveolar dead-space ventilation.
- Careful examination of a capnogram allows the detection of various abnormalities related to the equipment or the patient.
- Although capnography can be used in awake, nonintubated patients, it is more accurate in anesthetized and intubated patients.

207.2 INTRODUCTION

Capnometry is defined as the measurement and display of carbon dioxide concentration in the respiratory gases on a monitor. Maximum inspired and expired carbon dioxide concentrations during a respiratory cycle are displayed. Capnography is defined as a graphic display or recording of carbon dioxide concentration versus time or expired volume during a respiratory cycle (carbon dioxide waveform or capnogram). Time capnograms are most common and will be the only ones discussed here; volume capnograms can be used to measure the dead-space volume. A capnograph thus provides more information than does a capnometer; the interpretation of waveforms gives indications on the status of the patient and, in some cases, of the equipment.

Capnography can be used to confirm endotracheal tube placement, to assess ventilation and carbon dioxide elimination in a noninvasive manner, and (in combination with blood gas analysis) to estimate alveolar dead-space ventilation. Capnography has also been used to monitor the efficacy of cardiopulmonary resuscitation.

207.3 NONDIVERTING AND DIVERTING MONITORS

Two types of capnographs are available: nondiverting (mainstream) and diverting (sidestream).[1] As its name indicates, a nondiverting capnograph measures carbon dioxide concentration directly in the breathing system, whereas a diverting device samples gas from the breathing system and measures the carbon dioxide concentration in that gas in the main unit. In the nondiverting monitors, the patient's respiratory gas passes through a chamber with two windows. The sensor (light source and detector) fits over that chamber. The sensor also contains a heater to prevent water condensation on the windows. Advantages of mainstream devices include fast response time, no requirement for scavenging gas, ease of calibration (with a sealed chamber containing gas of known carbon dioxide concentration), and use of few disposable items. Disadvantages include the necessity to place the sensor near the patient (usually at the endotracheal tube connection), increase in apparatus dead space, potential for leaks, disconnection, or obstructions, potential for the sensor to become dislodged from the chamber, exposure of the sensor to damage, and measurement of carbon dioxide only.

In diverting monitors, the sensor is located in the main unit, remote from the breathing system. A pump samples respiratory gas at a constant flow, via sampling tubing. Advantages include minimal added dead space, lightweight patient interface, potential for the measurement of multiple gases, and possibility of use in places where the monitor needs to be remote from the patient. Disadvantages include potential for sampling problems, delayed response (especially with long sampling tubing), removal of gas at a given rate from the circuit, necessity to scavenge gas, potential for change in gas composition (depending on technology used), need for calibration gas, and potential for gas mixing in the sampling tubing (especially if the tubing is long).

207.4 TECHNOLOGY

Various techniques can be used to measure the concentration of carbon dioxide in the expired gas. These include infrared absorption, mass spectrometry, and Raman scattering.[1]

Infrared absorption is the most widely used technique. This technique is based on the concept that gases that have two or more dissimilar atoms in the molecule have unique and specific absorption spectra of infrared light. Infrared absorption can therefore be used to measure not only carbon dioxide but also nitrous oxide and the halogenated anesthetics.

Infrared monitors have a short warm-up time, and a quick response time, allowing them to measure inspired and expired concentrations. There is, however, some overlap between the absorption of carbon dioxide and nitrous oxide, and older devices need to be manually compensated when nitrous oxide is used. Water vapor must be removed from the expired gas (e.g., using Nafion tubing, water traps) because it absorbs infrared light at many wavelengths. Infrared absorption is the only technique available in nondiverting (mainstream) devices. It is also available in many diverting units.

Mass spectrometry is not used commonly to measure carbon dioxide concentration in respiratory gases. The mass 875

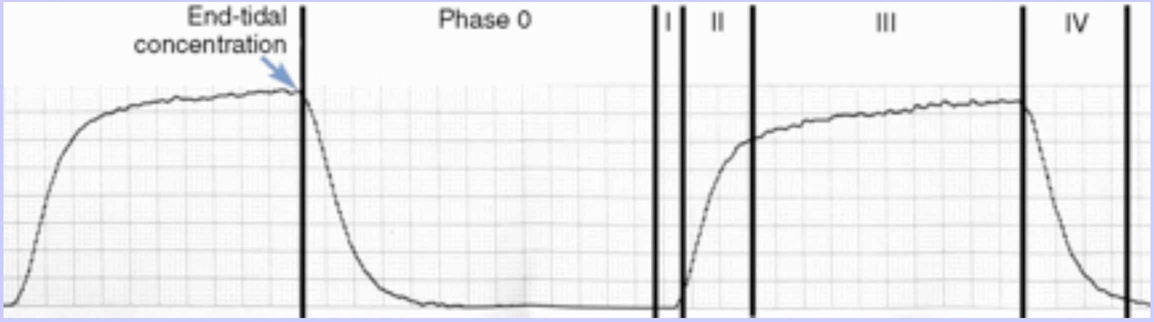
876 spectrometer spreads gases and vapors of different molecular weights into a spectrum, according to their mass-to-charge ratios. By designing the device properly, it is then possible to direct these different gases and vapors toward targets that can count the number of molecules. The mass spectrometer can be used to measure not only carbon dioxide, but also oxygen, nitrogen, nitrous oxide, and the volatile anesthetic agents. Depending on the type of mass spectrometer, measurement of a new agent may require hardware or software adaptation. Mass spectrometry can be used to measure gas concentration from one or several locations (up to 31). The device measures gases as concentrations (contrary to infrared analyzers and Raman spectrometers, which measure partial pressures), and therefore assumes that the sum of the gases it measures equals 100%. This may result in errors if a gas that is not measured is present in significant concentrations.

The basis of Raman spectrometry is that when laser light interacts with a gas molecule that has interatomic bonds, some of its energy is converted into vibrational and rotational modes, and a fraction of that energy is reemitted at various wavelengths characteristic of the molecule. Venkata Raman won the Nobel Prize in physics in 1930 for the discovery of this phenomenon. Raman scattering is used in one clinical monitor: the Ra scal II. This device measures oxygen, nitrogen, carbon dioxide, nitrous oxide, and up to five anesthetic agents. It has a fast response time and a very fast startup time. It requires little maintenance and is very accurate.

207.5 PHYSIOLOGY

A normal time capnogram can be divided into five phases (Figure 207-1).[1,2] Phase 0 corresponds to inspiration, and no carbon dioxide should be measured during that phase. Phase IV is the early part of inspiration, when carbon dioxide–free gas starts entering the airway. Some authors include phase IV in phase 0, or in phase III. Expiration is divided into the three remaining phases: I is early expiration, corresponding to the emptying of the anatomical dead space (no carbon dioxide should be measured); II is a rapidly changing mixture of alveolar and dead-space gas, resulting in a steep increase in measured carbon dioxide concentration; and III is the alveolar plateau, during which alveolar concentration of carbon dioxide is measured. The plateau usually has a slight increasing slope. The maximal concentration reached at the end of the plateau is the end-tidal concentration and is assumed to best represent alveolar carbon dioxide concentration (because gas sampled at that time is almost pure alveolar gas). In turn, alveolar carbon dioxide concentration in normal patients is only slightly lower than arterial carbon dioxide concentration. Therefore, assuming that no significant respiratory or cardiovascular abnormality is present and accurate end-tidal measurements are made, capnography allows continuous, noninvasive assessment of partial pressure of arterial carbon dioxide ($PaCO_2$).[2]

Figure 207-1 Normal capnogram.



Arterial PCO_2, and therefore end-tidal PCO_2, result from the balance between carbon dioxide production and carbon dioxide elimination (i.e., alveolar ventilation). Therefore changes in PCO_2 occur only if either production or elimination changes without associated changes in the other component. Because carbon dioxide is the main factor controlling breathing, in a normal, awake animal any change in carbon dioxide production will induce a proportional change in alveolar ventilation, so that PCO_2 remains constant. However, in anesthetized animals, or in animals with respiratory, muscular, or neurologic disease, this response to changes in carbon dioxide production may be lost to a variable extent, so that changes in carbon dioxide production may not result in compensatory changes in carbon dioxide elimination, the result being changes in PCO_2. Anesthesia and disease may also alter the normal response to carbon dioxide, so that alveolar ventilation may change (usually decrease) in absence of changes of carbon dioxide production, resulting in changes (usually increases) in PCO_2.[2]

The main information contained in a time capnogram includes: the inspired carbon dioxide concentration, the respiratory rate, and the end-tidal carbon dioxide concentration which, in most cases, is representative of arterial PCO_2. Abnormalities of the shape of a capnogram can provide additional information.[2,3]

As mentioned above, the gradient between end-tidal PCO_2 and arterial PCO_2 is normally small (less than 5 mmHg in small animal species). Increased dead-space ventilation (i.e., ventilation of alveoli that are not perfused) will increase this gradient. Causes of increased dead-space ventilation include ventilation-perfusion scattering and decreased pulmonary blood flow (e.g., pulmonary thromboembolism, low cardiac output). In these situations, a larger gradient between end-tidal and arterial PCO_2 may exist, so that end-tidal PCO_2 cannot be used to estimate arterial PCO_2 (but changes in end-tidal PCO_2 usually still correlate with changes in arterial PCO_2).

207.6 CAPNOGRAM INTERPRETATION

Even though capnography can be used during spontaneous ventilation, in awake or anesthetized patients, it is most useful during mechanical ventilation. It indeed provides a breath-by-breath monitoring of the adequacy of ventilation, and it allows the assessment of the response to changes in ventilator settings without having to sample arterial blood. 876 877 Although arterial blood gas analysis remains the gold standard to assess ventilation, capnography has two major advantages: it provides continuous versus intermittent monitoring, and it is not invasive. It is the only tool used clinically in animals that gives a continuous estimate of $PaCO_2$. Besides noninvasive assessment of $PaCO_2$, a capnogram allows the detection of various abnormalities pertaining to the equipment or patient.

207.6.1 Equipment

Increased apparatus dead space, rebreathing with a circle system (e.g., faulty unidirectional valve, exhausted carbon dioxide absorbent), and rebreathing with a nonrebreathing system (inadequate fresh gas flow, leak or disconnection of the inner tubing of Bain circuit) will all result in an elevated baseline, increased inspired PCO_2 and, if ventilation does not change, increased end-tidal PCO_2. The end-tidal-to-arterial PCO_2 gradient will be normal or decreased. The slope of phase IV usually is decreased.

Obstruction to expiration is detected by a decrease in the slope of phase II, an increase in the slope of phase III, and sometimes a decrease in end-tidal PCO_2 (if inspiration starts before expiration is complete).

Inadequate sealing around the endotracheal tube usually results in low, non-0 end-tidal readings.

207.6.2 Patient

Changes in carbon dioxide production without associated changes in alveolar ventilation will result in changes in end-tidal PCO_2, with a normal waveform, no inspired carbon dioxide, and a normal end-tidal-to-arterial PCO_2 gradient. Common causes of increased carbon dioxide production (and increased end-tidal PCO_2) include pain, anxiety, shivering, seizures, hyperthermia, administration of sodium bicarbonate, and carbon dioxide absorption from the peritoneal cavity during laparoscopy.

Apnea obviously results in the absence of a waveform. Hyperventilation results in a decrease in end-tidal PCO_2, with an otherwise normal waveform, no inspired carbon dioxide, and a normal end-tidal-to-arterial gradient. Hypoventilation results in opposite changes. Upper airway obstruction results in changes similar to those described for equipment obstruction.

Decreased transport of carbon dioxide to the lungs (e.g., decreased cardiac output, pulmonary thromboembolism) will result in decreased end-tidal PCO_2, normal capnogram, no inspired carbon dioxide, and an increased end-tidal-to-arterial PCO_2 gradient. Cardiac arrest results in a sudden decrease of end-tidal PCO_2 to 0 or near-0 values. Capnography can be used to monitor the efficiency of cardiopulmonary resuscitation by observing the return of carbon dioxide in the expired gas (related to the return of pulmonary blood flow). End-tidal carbon dioxide values during cardiopulmonary resuscitation have been reported to correlate with resuscitation success (the higher the values, the better the chances of successful resuscitation).

Many types of lung disease result in a scattering of time constants in different areas of the lung. In turn, this results in sequential emptying of “faster” and “slower” alveoli. This will be illustrated on the capnogram by an increased slope of phase III. Bronchoconstriction (asthma, bronchospasm) is a typical cause of prolonged expiration (phases II and III) and decreased slope of phase II–increased slope of phase III.

Cardiogenic oscillations can be seen sometimes on a capnogram. These are small oscillations in phase IV. The slope of this downstroke is also decreased. The frequency of these oscillations corresponds to heart rate. Cardiogenic oscillations are due to gas movement in the airway caused by the heart beat.

A “curare cleft” is a decrease in carbon dioxide concentration during the alveolar plateau. This is due to a spontaneous inspiratory effort in mechanically ventilated patients.

Graphic examples of normal and abnormal capnograms can be found at http://www.capnography.com.

207.7

SUGGESTED FURTHER READING*

JA Dorsh, SE Dorsh: Gas monitoring. In JA Dorsh, SE Dorsh (Eds.): *Understanding anesthesia equipment*. ed 4, 1998, Williams & Wilkins, Baltimore, *An excellent textbook on anesthesia equipment, including monitoring devices*.

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* See the CD-ROM for a complete list of references

208 Chapter 208 Blood Gas and Oximetry Monitoring

Laurie Sorrell-Raschi, DVM, DACVA

208.1 KEY POINTS

- Interpretation of blood gases requires an understanding of acid-base and respiratory physiology.
- There are six basic steps to follow when interpreting arterial blood gases.
- Pulse oximetry provides a noninvasive means of monitoring oxygenation.
- The final step to blood gas analysis is to evaluate the significance of the findings as they relate to the patient.

208.2 INTRODUCTION

Perhaps Rawson and Quinlan said it best when they asserted that, “the interpretation of blood gas analysis may be very difficult because it requires an understanding of not only the physiology of acids and bases, but also the physiology of ventilation and gas exchange, the dynamics of electrolyte and water movement, plasma composition, and the renal mechanisms of hydrogen ion, electrolyte and water excretion.”[1] Blood gas analysis is, however, an invaluable tool for assessing the physiologic status of critically ill patients. It is necessary, therefore, to develop a method for efficiently and effectively evaluating this information to treat the patient appropriately.

Although a thorough description of acid-base regulation and blood gas analysis is beyond the scope of this chapter (the reader is directed to several excellent references for a more detailed description of these subjects[2-9]), what follows is a brief overview of acid-base physiology and a practical method of interpreting blood gases (see Chapter 59, Acid-Base Disturbances).

208.3 HYDROGEN IONS

The proton is one of the basic chemical units of matter. The term *proton* has become synonymous with the term *hydrogen ion* or H^+ in medical physiology. This electrolyte is the end product of many metabolic processes within the body and the normal H^+ concentration ($[H^+]$) in the extracellular fluid is maintained at around 40 nanoequivalents per liter. Comparatively, the normal concentrations of most physiologically important electrolytes (e.g., Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-) are present in the body in the range of milliequivalents per liter.

Although hydrogen ion concentration $[H^+]$ is one millionth the concentration of other electrolytes in the body, its regulation is of paramount importance to normal homeostasis. Hydrogen ions are highly reactive and therefore readily interact with dissociable moieties on proteins. Because proteins play a major role in all biologic functions, alterations in protein structure or function as a result of changes in $[H^+]$ within the body can have catastrophic effects on biologic homeostasis.

208.4 BUFFERS

Changes in [H^+] are opposed by buffer systems within the body. These systems consist of a buffer pair of an acid (H^+ donator) and its conjugate base (H^+ acceptor) as follows:

$$\underset{acid}{HA} \leftrightarrow H^+ + \underset{base}{A^-}$$

The law of mass action states that the velocity of a reaction is proportional to the concentration of reactants on either side of the equation and their dissociation constants (*k*):

$$\frac{k_1}{k_2} = K_a = \frac{[H^+][A^-]}{[HA]}$$

Weak acids and their conjugate bases constitute the most effective buffer pairs in the body, because they are more capable of accepting or donating H^+ in the presence of changes in H^+ load compared with strong acids, which are highly dissociated in many biologic fluids.

208.5 HENDERSON-HASSELBACH

In the early 1900s, L.J. Henderson revolutionized the study of acid-base physiology by noting that CO_2 (a primary end product of cellular metabolism) combines with H_2O in the presence of carbonic anhydrase to form H_2CO_3 (carbonic acid). This acid will then further dissociate into its conjugate base, bicarbonate (HCO_3^-), and H^+:

$$CO_2 + H_2O \overset{carbonic\ anhydrase}{\leftrightarrow} H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

By applying the laws of mass action and because H_2CO_3 exists in equilibrium with dissolved CO_2, Henderson substituted the value of dissolved CO_2 in his equation. Thus:

$$[H^+] = K_a\left(\frac{[CO_2]}{HCO_3^-}\right)$$

This equation had major implications because it not only described one of the first known buffer pairs (H_2CO_3 and 878
HCO_3^-), but also illuminated a process by which the body could buffer changes in H^+ load, namely ventilation. 879
Later Hasselbach would add further utility to the equation by substituting the partial pressure of CO_2 in blood (PCO_2) for dissolved CO_2 and applying Sorenson's concept of pH (the negative logarithm of [H^+]) by putting the equation in logarithmic notation:

$$pH = pK_a + log\left(\frac{HCO_3^-}{PCO_2 \times SC}\right)$$

where pKa = the logarithm of the ionization constant K_a for H_2CO_3, and SC = the solubility coefficient of CO_2 in blood (0.03).

This is the classic Henderson-Hasselbach equation.

208.5.1 Regulation of pH

On a daily basis, pH changes within the body are opposed by multiple complex processes which, for the sake of simplicity, can be presented as (1) the actions of intracellular and extracellular buffering systems (chemical buffering), (2) modulation of ventilation (physiologic buffering), and (3) renal clearance. All body fluids contain buffer systems. Of these systems, hemoglobin, phosphate, protein (predominately intracellular buffers), bone, and HCO_3^- (predominately extracellular buffer), the HCO_3^- system is of utmost importance. The reasons are twofold. Not only is the HCO_3^- buffering system capable of responding to an acute change in $[H^+]$ within seconds of an acid load, but its role in the $HCO_3^- - H_2CO_3 - CO_2$ equilibrium equation allows changes in pH to be further modulated by changes in ventilation. This “open system” greatly enhances the buffering capacity of the HCO_3^- system and is capable of buffering changes in pH within minutes of an acid or alkali load. Finally, the kidneys play a major role in maintaining pH by increasing or decreasing acid elimination in the urine. This system takes hours to days to reach completion, but is the most capable of all the processes for returning the body's pH to normal.

208.6 BLOOD GAS ANALYSIS: GETTING STARTED

Although blood gas analysis may be performed on venous blood (see Venous Blood Gases later in this chapter), arterial blood gas analysis yields information about oxygenation as well as ventilation and acid-base disorders and is preferentially performed, when possible. There are several potential sites for arterial puncture (the dorsopedal artery, the digital artery in the front paw, the auricular artery, the lingual artery, the femoral artery). However, the dorsopedal artery is chosen most often because of its size, superficial location, and ease of ensuring adequate hemostasis.

A small amount of local anesthetic such as 0.05 to 0.1 ml of 2% lidocaine injected subdermally 2 to 3 minutes before sampling may aid in restraint. An arterial catheter may allow for repeated blood gas sampling with less stress for the patient. Blood should be drawn into a syringe coated with sodium or lithium heparin (1000 U/ml), keeping in mind that heparin is acidic and excessive amounts in the syringe may have a detrimental effect on blood gas values.[10] Any air bubbles should be expelled from the sample, and the sample corked or attached to a stopper to prevent further exposure to room air, which could decrease the sample's PCO_2 to zero and sample partial pressure of oxygen (PO_2) level to that of room air (150 mmHg at sea level).[10] The sample should be analyzed immediately or held in an ice- water bath at 4° C (up to 2 hours) to minimize the effects of cellular metabolism on sample pH, PCO_2, and PO_2.[11]

Table 208-1 Normal Arterial Blood Gas Values for Dogs and Cats[14,15]

Parameter	Dog Value	Cat Value
pH	7.39 ± 0.03	7.39 ± 0.08
$PaCO_2$ (mm Hg)	37 ± 3	31 ± 6
PaO_2 (mm Hg)	102 ± 7	107 ± 12
HCO_3^- (mEq/L)	21 ± 2	18 ± 4
Base excess (mEq/L)	−2 ± 2	−2 ± 2

HCO_3^-, Bicarbonate; *$PaCO_2$*, partial pressure of arterial carbon dioxide; *PaO_2*, partial pressure of arterial oxygen.

208.6.1 Temperature Correction

Whether or not to correct blood gas values for temperature remains a controversial subject in both human and veterinary medicine. The issue centers around the hypothesis that as temperature changes, blood gas solubility also changes, and blood gas values may be altered as well. The pH-stat strategy suggests correcting blood gas values for patient temperature and maintaining the corrected values within accepted norms for pH and PCO_2. The α-stat strategy assumes that hemoglobin's buffering capacity, which is related to the ionization of the imidazole group of histidine residues, is not affected by temperature changes. Under these circumstances there would be no need to temperature correct blood gas values.

According to the literature, most attempts at critically applying one strategy over the other have been performed in the context of providing improved neurologic outcomes in human patients after coronary artery bypass surgery and have shown differing and confounding results.[12,13] There is no clear indication that routine temperature correction in the clinical setting is necessary. It is up to the clinician, therefore, to decide which strategy seems most reasonable and apply that strategy consistently to serial sampling.

208.6.2 Step-by-Step Acid-Base Analysis

208.6.2.1 Number 1: Look at the pH

Table 208-1 shows normal arterial blood gas values in dogs and cats.[14,15] As pH varies inversely with $[H^+]$, any process that increases H^+ load will decrease pH and produce acidosis. Conversely, any process that decreases $[H^+]$ will tend to increase pH and produce alkalosis. The terms *alkalemia* and *acidemia* imply that blood pH is outside the normal range, which may or may not be true depending on the nature of the acid-base disorder and the effectiveness of organism's compensatory mechanisms.

According to the Henderson-Hasselbach equation, the pH has two components: a ventilatory component (PCO_2) and a metabolic component HCO_3^-). The pH varies directly with changes in the metabolic component 879 and inversely with changes in the respiratory component. It would follow that pH changes produced by one component may be opposed by opposite changes in the other component. For instance, to compensate for a respiratory acidosis the organism will attempt to increase the concentration of HCO_3^- in the blood. The compensation may be strong, but rarely is it complete, and overcompensation does not normally occur.[4]

Table 208-2 Acid-Base Disturbances

Disorder	pH	Primary Derangement	Expected Compensation
Respiratory acidosis	↓	↑ PCO_2	↑ HCO_3^-
Respiratory alkalosis	↑	↓ PCO_2	↓ HCO_3^-
Metabolic acidosis	↓	↓ HCO_3^-, –BE	↓ PCO_2
Metabolic alkalosis	↑	↑ HCO_3^-, +BE	↑ PCO_2

BE, Base excess; HCO_3^-, bicarbonate; PCO_2, partial pressure of carbon dioxide.

Table 208-3 Expected Compensation for Acid-Base Disorders

Disturbance	Clinical Guide for Compensation
Metabolic acidosis	Expected PCO_2 = 35 – [(22 – HCO_3) × 0.7] ± 3 mm Hg
Metabolic alkalosis	Expected PCO_2 = 35 + [(22 – HCO_3) × 0.7] ± 2 mm Hg
Acute respiratory acidosis	Expected HCO_3^- = 22 + [(PCO_2 – 35) × 0.15] ± 2 mEq/L
Chronic respiratory acidoses	Expected HCO_3^- = 22 + [(PCO_2 – 35) × 0.35] ± 2 mEq/L
Acute respiratory alkalosis	Expected HCO_3^- = 22 + [(PCO_2 – 35) × 0.25] ± 2 mEq/L
Chronic respiratory alkalosis	Expected HCO_3^- = 22 + [(PCO_2 – 35) × 0.55] ± 2 mEq/L

HCO_3^-, Bicarbonate; PCO_2, partial pressure of carbon dioxide.

208.6.2.2

Number 2: What's Happening With Ventilation?

Control of ventilation arises from respiratory centers within the brainstem that are sensitive to CO_2-induced changes in cerebral pH.[16] Arterial CO_2 levels are held steady by balancing minute ventilation with metabolic production of CO_2; however, normal ventilatory response to changes in PCO_2 are so sensitive that a 1–mmHg change in PCO_2 can quadruple minute ventilation. Although ventilation may exceed the production of CO_2, it is unlikely that CO_2 production exceeds ventilatory capacity in normal animals.

Respiratory acidosis therefore is almost always caused by some aspect of ventilatory failure.[16] Tables 208-2, 208-3, and Box 208-1 show the most common causes of respiratory acidosis and alkalosis in dogs and cats and the expected acid-base changes that subsequently occur.[6,17-19] It is important to note that although dogs and cats respond similarly to acute respiratory acidosis, there is some question as to whether cats adjust as well to chronic respiratory acidosis as dogs. This may be because cats lack the adaptive process of urinary ammoniagenesis that allows dogs to bring their pH very close to normal in longstanding chronic respiratory acidosis (>30 days).

208.6.2.2.1

Box 208-1 Causes of Respiratory-Induced Acid-Base Disorders

208.6.2.2.1.1

Causes of Respiratory Acidosis

Pulmonary and small airway disease

Respiratory center depression

Neuromuscular disease

Restrictive extrapulmonary disorders

Large airway obstruction

Marked obesity

Ineffective mechanical ventilation

208.6.2.2.1.2

Causes of Respiratory Alkalosis

Iatrogenic (mechanical ventilation)

Hypoxemia

Pulmonary disease without hypoxemia

Centrally mediated hyperventilation

Pain, anxiety, fear

Also of note is that the normal renal response to respiratory acidosis and alkalosis (namely HCO_3^- retention and excretion, respectively) will take several hours to days to correct after correction of the primary respiratory acid-base disorder. The patient may require treatment of the electrolyte changes (chloride in particular) that accompany the renal response to respiratory acid-base disorders before full correction to baseline HCO_3^- values can be achieved.[6,9]

208.6.2.3 Number 3: What's Happening With the Metabolic Indexes?

Metabolic acid-base disturbances are among the most common acid-base disorders described in veterinary medicine. A prominent feature of metabolic disturbances is a change in the HCO_3^- level, but this should not be the sole indicator of a metabolic disturbance because HCO_3^- also changes with alterations in PCO_2. Consequently, the concept of buffer base is used to define metabolic disorders.

Base excess (BE) is derived from the whole blood buffer curve developed by Siggaard-Anderson and is defined as the amount of acid or base necessary to titrate a 1 liter of blood to a pH of 7.4 if PCO_2 is held constant at 40 mmHg.[21,22] Because PCO_2 is held constant, the BE is reflective of the nonrespiratory component of the organism's buffer system. Tables 208-2, 208-3, and Box 208-2 show the most common causes of metabolic acidosis and alkalosis, as well as relevant acid-base responses.* The question remains as to whether cats typically have the expected ventilatory response to metabolic acidoses. There is experimental evidence to suggest that they do not.[7]

* References 5, 7, 19, 20, 23, 24.

208.6.2.4 Number 4: Is There One Problem or Many?

One of the hardest parts of acid-base analysis can be deciding what the primary disorder is. A good rule of thumb is that the pH of the sample will reflect the primary disorder. This sounds simple, but it becomes more and more complicated as compensation and multiple disturbances occur. Various acid-base disturbances may occur simultaneously, except for a respiratory alkalosis and acidosis, which are mutually exclusive. Multiple primary disorders that change the pH in the same direction are readily apparent (see Table 208-2). Multiple primary disorders that change the pH in different directions can be distinguished from a single primary disorder with compensation by determining the expected compensation in PCO_2, HCO_3^-, or pH and comparing it with the observed compensation (see Table 208-3). If the two are not equal, there are most likely multiple primary disorders.[3,7–9]

208.6.2.4.1

Box 208-2 Causes of Metabolically Induced Acid-Base Disorders

208.6.2.4.1.1

Causes of Metabolic Acidosis

208.6.2.4.1.1.1

Normochloremic Causes

Lactic acidosis

Ketoacidosis

Toxins

Renal failure

208.6.2.4.1.1.2

Hyperchloremic Causes

Gastrointestinal losses

Renal

Other

208.6.2.4.1.2

Causes of Metabolic Alkalosis

208.6.2.4.1.2.1

Chloride-Responsive Causes

Vomiting

Diuretic therapy

Correction of respiratory acidosis

208.6.2.4.1.2.2

Chloride-Resistant Causes

Primary hyperaldosteronism

Hyperadrenocorticism

Overadministration of alkaline fluids

Other

208.6.2.5

Number 5: What's Happening With Oxygenation?

Oxygen is necessary for aerobic metabolism. Hypoxia occurs whenever oxygen levels in the blood are low enough to cause abnormal organ function. Hypoxemia occurs when oxygen levels in the blood are too low to meet metabolic demands.[16]

PaO_2 is the partial pressure of oxygen dissolved in the arterial blood (plasma). It is the most common blood gas parameter used to monitor the progress of patients with respiratory disorders. Normal PaO_2 values for a dogs and cats breathing room air (21% O_2) are shown (see Table 208-1). A PaO_2 less than 80 mmHg is considered hypoxemia.[16] Although PaO_2 is very useful and reliable, it is dependent on the alveolar partial pressure of oxygen (PAO_2) according to the alveolar gas equation:

$$PAO_2 = \left(P_B - PH_2O\right) FiO_2 - \frac{PaCO_2}{R}$$

where P_B = the barometric pressure, PH_2O = the partial pressure of water vapor in the air at a given barometric pressure, FiO_2 = the fractional inspired concentration of oxygen, and R = the respiratory quotient that is the ratio of oxygen consumption to CO_2 production (0.78 to 0.92 in dogs).[25] In normal healthy lungs, oxygen diffuses readily from the lungs to the arterial circulation. The PaO_2 should be within 10 mm Hg of the PAO_2 in animals breathing room air and up to 100 mm Hg when the FiO_2 is 100%. It is possible for normal dogs living at high altitudes to have a PaO_2 of 60 mm Hg (PAO_2 and PaO_2 are decreased with low barometric pressure). Similarly, a PaO_2 reading of 100 mm Hg is not acceptable if a dog is anesthetized and breathing 100% oxygen (the PaO_2 should be 500 mm Hg).

The alveolar-arterial (A-a) gradient is calculated as a way to quantify the efficiency of gas exchange. At O_2 concentrations of 21%, the A-a gradient is expected to be less than 10 mm Hg, however, at O_2 concentrations of 100% the A-a gradient can normally be up to 100 mm Hg.[26-28] Consequently, the patient's FiO_2 must always be considered when evaluating the A-a gradient.

The a:A ratio and PaO_2-to-FiO_2 ratio are two other indexes of hypoxemia. Of the two, the PaO_2-to-FiO_2 is the easiest to calculate and shows the most reasonable stability across variable inspired oxygen concentrations. Normal values for the PaO_2-to-FiO_2 ratio should be greater than 400 mm Hg. Values below 300 mm Hg indicate severe defects of gas exchange. Values less than 200 mm Hg may indicate acute respiratory distress syndrome.[26,28]

The PaO_2-to-FiO_2 ratio demonstrates some dependency on $PaCO_2$, but this diminishes at an FiO_2 higher than 50%, which is usually the point at which this ratio is likely to be employed.

The oxygen content ml/dl (CaO_2) value is a calculated value that is included with many blood gas analyses. It is an assessment of the total amount of oxygen carried in the blood. It includes the oxygen dissolved in the plasma and bound to hemoglobin and is an important measure of the oxygen carrying capacity of the blood as follows:

$$CaO_2 = (PaO_2 \times 0.003) + (1.34 \times \text{Hb} \times SaO_2)$$

where 0.003 = the solubility of oxygen in plasma, 1.34 = the amount of oxygen in milliliters that each gram of hemoglobin (Hb) can hold if it is 100% saturated with O_2, and SaO_2 = oxygen saturation. Normal CaO_2 is 20 ml of O_2 per dl of blood.

Oxygen saturation (SaO_2) is a measure of the percentage of the heme groups in an arterial blood sample that are occupied by oxygen molecules as measured using a co-oximeter. The relationship between SaO_2 and PaO_2 is sigmoidal, with maximum saturation seen above a PaO_2 of 100 mm Hg. Most blood gas analyzers do not measure SaO_2 and instead calculate it using a nomogram derived from the oxygen dissociation curve. Under normal circumstances this has few drawbacks; however, if dysfunctional hemoglobin species (such as carboxyhemoglobin, methemoglobin, sulfhemoglobin, and carboxy sulfhemoglobin) or fetal hemoglobin are in circulation, it is important to measure oxygen saturation with a co-oximeter. These devices use four wavelengths of light passed through a blood sample to distinguish between oxygenated hemoglobin and the other types of hemoglobin not carrying oxygen or unable to contribute to gas exchange.[3]

208.6.2.5.1 Pulse Oximetry

Pulse oximeters are bedside monitors that measure the SpO_2 rather than the SaO_2 and take advantage of the simple principle used by co-oximeters: blood that is oxygenated is a different color than blood that is not well oxygenated. When light is passed through a tissue bed it is possible to determine the oxygen saturation 881
within that tissue. Deoxygenated hemoglobin absorbs more red light, and oxygenated blood absorbs more 882
infrared light. By using two wavelengths (940 and 660 nm), a high light transmittance speed, fast sample rate, and a microprocessor that filters any nonpulsatile data as nonarterial blood flow, it is possible to build a monitor capable of providing a noninvasive measure of oxygenation.[29]

Pulse oximetry is useful for several reasons. It provides an inexpensive, noninvasive means of monitoring oxygenation that is well tolerated and reliable in dogs and cats, when more invasive monitoring is either unwarranted, undesirable, impossible to obtain, or some combination thereof.[30–34] The machines are small, quiet, portable, can be used for extended periods, and can be used as an indirect measure of perfusion.

As with most screening equipment, there are drawbacks. Pulse oximetry probes typically perform well on the tongue, but this location is difficult or impossible to use in a conscious patient. The probes may be placed on the shaved skin of the lip, pinna, toe web, flank, or tail, but many conscious patients will not readily tolerate it. Additionally, pulse oximetry readings can be affected by bright overhead lights, vasoconstriction, dark skin pigment, hypothermia, and hypoperfusion. Abnormal hemoglobin will also cause the machine to read inaccurately. Unlike co-oximeters, pulse oximeters cannot distinguish dysfunctional hemoglobins (i.e., carboxyhemoglobin, methemoglobin, sulfhemoglobin, and carboxy sulfhemoglobin) from normal hemoglobin. Carboxyhemoglobin will absorb infrared light similarly to oxygenated hemoglobin and will provide falsely high SpO_2 readings. Methemoglobin on the other hand absorbs both wavelengths of light equally well. In the presence of this hemoglobin species the pulse oximeter will default to a reading of 85%, reading high or low depending on the patient's actual saturation. Most importantly, pulse oximetry gives little information about the efficiency of gas exchange. An SpO_2 of 100% in a patient breathing an FiO_2 of 100% does not evaluate whether the patient's PaO_2 is 500 mmHg or 100 mmHg. It is more appropriate to perform arterial blood gas analysis anytime that precise information is needed regarding the patient's oxygenation status.

208.6.2.6 Number 6: Looking at the Whole Picture

The final step in blood gas analysis is to fit the analysis to the patient. Make sure the conclusions fit the clinical picture. Multiple ancillary techniques from the anion ion gap,[5,7] or the use of electrolyte shifts to qualify metabolic acid-base disturbances, to Stewart's concept of strong ion differences[8,35] (acid-base disturbances explained as a series of polynomial equations) are now being used to further refine acid-base analysis when the numbers do not fit the clinical picture.

208.6.3 Venous Blood Gases

Venous blood gases are often more simple to obtain than arterial gases. The PCO_2 of venous blood is usually 4 to 6 mmHg higher and the pH is usually 0.02 to 0.05 units lower than those of arterial blood. In stable hemodynamic states venous blood gases may be used for clinical assessment of acid-base disorders.[15,36] Peripheral venous PO_2 values are not representative of arterial oxygen values; however, the blood from veins in the tongue or the claw may be “arterialized” under certain conditions and used for this purpose.[15,37-39] A venous PO_2 of less than 30 mmHg may suggest poor tissue oxygenation and should be investigated further.

208.7 SUGGESTED FURTHER READING*

HA deMorais, SP DiBartola: Ventilatory and metabolic compensation in dogs with acid-base disturbances. *J Vet Emerg Crit Care*. **1**, 1991, 39, *Provides useful information about compensatory mechanisms with acid-base disturbances*.

SP DiBartola: Introduction to acid-base disorders. In SP DiBartola (Ed.): *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 3, 2006, Saunders, St Louis, *Excellent introduction to acid-base disorders*.

SC Haskins: Interpretation of blood gas measurements. In LG King (Ed.): *Textbook of respiratory disease in dogs and cats*. ed 1, 2004, Saunders, St Louis, *Very good reference chapter. More physiologically oriented than practically oriented*.

JC Hendricks, LG King: Practicality, usefulness, and limits of pulse oximetry in critical small animal patients. *J Vet Emerg Crit Care*. **3**(1), 1993, 512, *Very complete and useful reference on the use and drawbacks of pulse oximetry in critically ill small animals*.

AE Wagner, WW Muir, RM Bednarski: A comparison of arterial and lingual and venous blood gases in anesthetized dogs. *J Vet Emerg Crit Care*. **1**(1), 1991, 14, *Good study with very practical information*.

See the CD-ROM for a complete list of references

209 Chapter 209 Intracranial Pressure Monitoring

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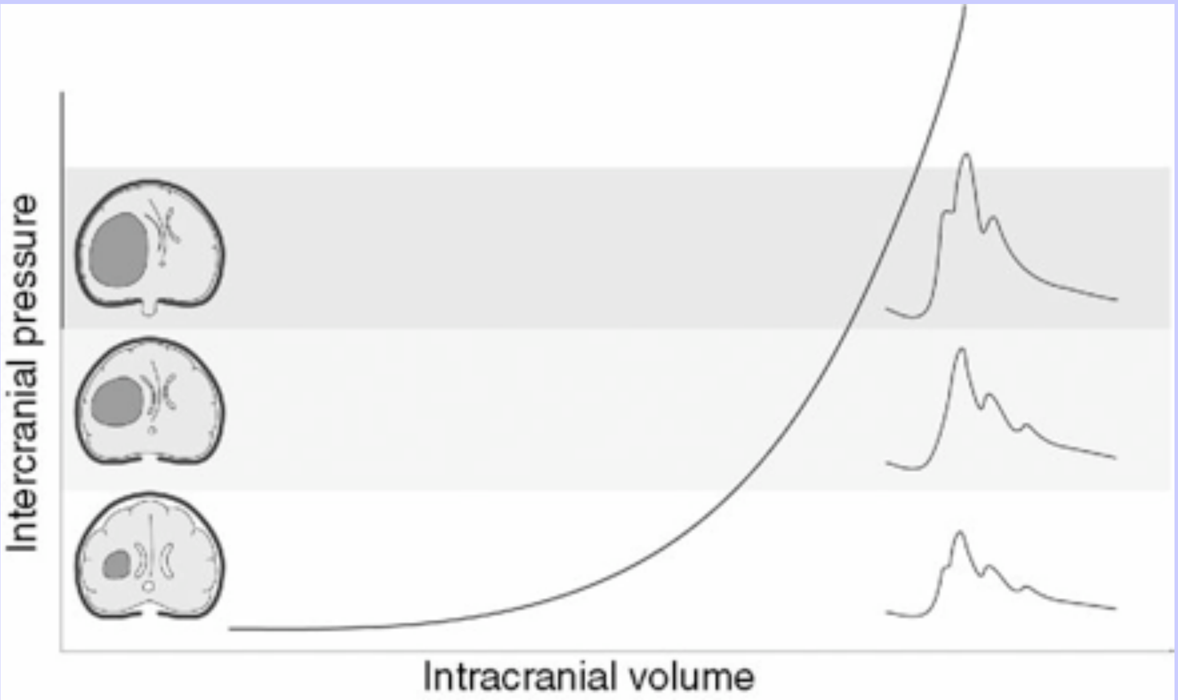
Figure 209-2 Intracranial pressure tracings of the pulse pressure waves are shown on the right. Alterations in the amplitude and shape of the waveforms occur with changes in intracranial pressure and compliance of the neural tissues are shown on the left. This may be used to estimate where a patient's condition is located on the pressure-volume curve.



209.1 KEY POINTS

- Maintaining adequate cerebral perfusion pressure (CPP) is considered the cornerstone of successful treatment of acquired brain injury.
- By monitoring intracranial pressure (ICP) and mean arterial blood pressure (MAP), the clinician can quantitatively assess CPP as expressed by the formula: CPP = MAP – ICP.
- Normal ICP varies between 5 and 10 mm Hg above atmospheric pressure in dogs and cats.
- Catheter tip ICP transducers (fiberoptic or miniature strain gauge) have been used with ease and accuracy in dogs and cats when placed subdurally or intraparenchymally in the brain.

- Monitoring ICP is most important in patients with intracranial hypertension from severe brain disease or head injury and in animals that are anesthetized or comatose.

209.2 INTRODUCTION

Acquired brain injury is a common neurologic emergency typically caused by head trauma, brain disease (tumors, meningoencephalitis, hypoxic injury), metabolic derangements, prolonged seizures, or surgical trauma. Increased intracranial pressure (ICP) often is associated with these processes and may affect outcome seriously. Because the intracranial contents (blood, cerebrospinal fluid [CSF], and brain parenchyma) are encased in a rigid container, there is limited space available for expansion of the contents. As volume increases in the cranial vault from any cause (edema, hemorrhage, mass), there must be a reciprocal decrease in the other volumes for ICP not to increase beyond limits compatible with life.[1,2]

When compensatory mechanisms in the brain are exhausted, ICP increases and cerebral blood flow is compromised, resulting in secondary injury. Secondary injury is a complex sequence of events that leads to further elevations in ICP, reduced cerebral blood flow, tissue hypoxia, and ischemia. This ultimately perpetuates neuronal death and may result in brain herniation.[1,2] Thus, secondary injury is a major contributor to the mortality of animals with acquired brain injury. The primary goal in the treatment of these animals is to minimize the impact of the secondary injury by appropriate and timely treatment to maintain adequate cerebral blood flow. In the clinical setting, cerebral blood flow is reflected most accurately by cerebral perfusion pressure (CPP). CPP is dependent on the mean arterial pressure (MAP) and the ICP, and this relationship is expressed by the formula: CPP = MAP – ICP.[1,2] By measuring the ICP, the clinician is able to assess whether CPP is maintained adequately in a patient with severe brain disease or injury.[3,4]

Although a growing number of studies in humans have suggested decreased mortality rates and improved long-term outcome with ICP-guided therapy, a randomized clinical trial showing that ICP monitoring improves outcome has not been done. The “Guidelines for the Management of Severe Traumatic Brain Injury” (published in 1995 and revised in 2007) outline the evidence-based recommendations for using ICP monitoring to improve the treatment and outcome from severe brain injury.[4] Similar guidelines and recommendations were published in 2004 for the management of severe brain injury in infants and children. As yet, no specific guidelines have been established in veterinary medicine for treating severe brain injury. The standard of care has been primarily that of repeated and careful assessments of an animal's neurologic status in an attempt to detect increases in ICP. Unfortunately, most clinical signs indicating life-threatening intracranial hypertension (ICH) occur as a result of damage to brain tissue, and therapies administered at this point often are ineffective. There are potential benefits gained by monitoring ICP, especially when one expects prolonged and/or life-threatening ICH (Box 209-1).[4,5]

209.2.1 Box 209-1 Benefits of Intracranial Pressure Monitoring

1 Allows assessment of actual ICP as well as fluctuations and overall trends in ICP

2 Allows optimization of cerebral perfusion pressure–guided therapy

3 Allows for early intervention

4 Reduces indiscriminate treatment of ICH

5 Allows assessment of the effects of treatment of ICH

6 Allows assessment when clinical monitoring is not possible (anesthetized or comatose animals)

7 Provides assessment of brain death (cerebral perfusion ceases once ICP exceeds diastolic blood pressure)

ICH, Intracranial hypertension; *ICP,* intracranial pressure.

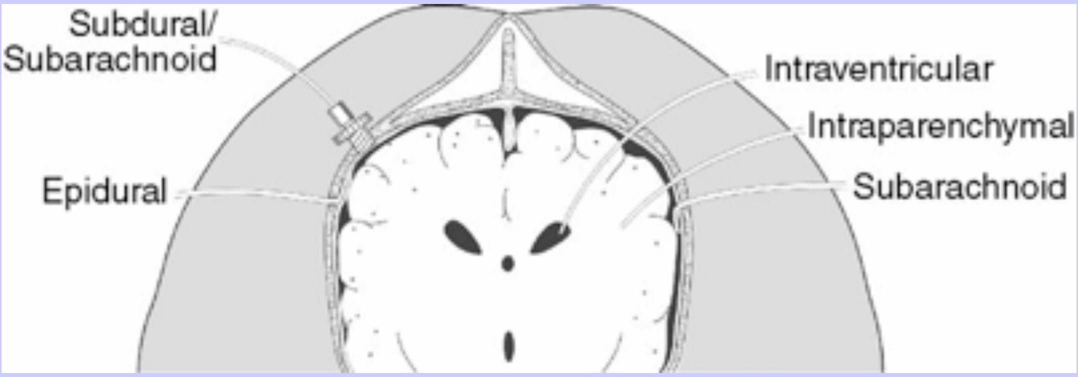
209.3 DETERMINATION OF INTRACRANIAL PRESSURE

209.3.1 Intracranial Pressure

ICP refers to the pressure exerted by the tissues and fluids against an inelastic cranial vault. The total pressure recorded when monitoring ICP is actually composed of several components[1,2]:

1. *Atmospheric pressure* results from the weight of the atmosphere on the brain; for example, a higher altitude results in a higher absolute ICP. Because ICP is always reported relative to the atmospheric pressure, this component is usually not taken into consideration.

Figure 209-1 Intracranial pressure monitoring locations.



2. *Hydrostatic pressure* is influenced by the orientation of the neuraxis relative to gravity (e.g., consider a giraffe versus a rat).
3. *Filling pressure* refers to the volume of fluid within the cranial vault and affects the compliance or “give” of the brain tissues.

209.3.2 Locations for Monitoring Intracranial Pressure in the Brain

ICP monitoring commonly is done through a burr hole in the skull or a craniectomy site. It can be measured directly or reflected through measurement of CSF pressure or brain tissue pressure.[2,3] CSF pressure measurements can be taken from the lateral ventricles or the cerebral subarachnoid space; brain tissue pressure measurements are taken intraparenchymally from within a cerebral hemisphere. Measurement of ICP from the brain's surface may be taken epidurally or subdurally over a cerebral convexity[1,2,4] (Figure 209-1).

Although there are very few data in veterinary medicine with respect to the role of ICP monitoring in patients with brain disease, several studies in animals have shown that ICP can be monitored accurately. Historically, CSF pressure was measured using a manometer and needle puncture of the cisterna magna. This method requires that the patient undergo general anesthesia and does not allow for ongoing ICP measurements needed to guide the clinician in treatment decisions. In addition, CSF pressures measured at the cisterna magna may not accurately reflect more compartmentalized elevations in ICP. In animals with global ICH, there is the added risk of brain herniation through the foramen magnum with this method.

209.3.3 Types of Intracranial Pressure Monitoring Devices

Pressure transducers convert ICP into a graded electrical signal that is recorded and displayed. They can be situated either intracranially or extracranially depending on the system used. Extracranial strain gauge type transducers communicate with the intracranial compartment via fluid-filled tubing and require that ICP measurements be taken at fixed reference points. Pressure transducers situated intracranially are incorporated into the tip of a catheter and implanted into one of several compartments of the brain. Some of the important considerations in choosing a transducer are listed in Box 209-2.[2-4]

209.3.3.1 Box 209-2 Considerations for Choosing an Intracranial Pressure Transducer

209.3.3.1.1 External Pressure Transducer

209.3.3.1.1.1 Pros

- Accurate
- May be recalibrated after insertion
- Minimal zero drift
- Less expensive

209.3.3.1.1.2 Cons

- Fluid couple may obstruct and give false readings
- Measurements must be taken at fixed reference points
- Allows little movement in awake animals
- Leakage may occur in the system

209.3.3.1.2 Internal Pressure Transducer

209.3.3.1.2.1 Pros

Allows freedom of movement

Accurate

Technically easy to place

209.3.3.1.2.2 Cons

Cannot be rezeroed after insertion

Some zero drift over time

More expensive

209.3.4 Intracranial Pressure Monitoring Systems

209.3.4.1 Ventriculostomy Catheter With External Transducer

The ventriculostomy catheter is a fluid-filled hollow tube that is inserted into the lateral ventricle, usually through a burr hole craniotomy. The catheter is connected to an external strain gauge transducer via fluid-filled pressure-resistant tubing. The transducer is leveled or zeroed at an external reference point that represents the level of the foramen of Monro in the brain. Strain gauge transducers convert mechanical pressure (or “strain”) into a graded electrical signal.[2-4] Thus changes in ICP cause changes in the pressure exerted on the diaphragm and hence strain on the sensor element. The electrical resistance that is generated is recorded and displayed.

Ventriculostomy catheters provide the most accurate reflection of ICP and have become the “gold standard” or reference standard for monitoring ICP. In addition to ICP measurements taken from the ventricle, CSF can be withdrawn as needed for treatment of elevated ICP. Because of this advantage, it is commonly used in humans. The external landmarks defining the trajectory for accurate placement of a ventriculostomy catheter are easily identified in humans, and the location of the lateral ventricle is reliably predicted most of the time. However, in dogs and cats, several anatomic considerations impede the feasibility of using this system clinically. These include the marked variation in skull size and shape among breeds of dogs, variation in the size, shape, and location of the lateral ventricles in the brain, and the presence of substantial musculature overlying the cranial vault and obscuring identifying bony landmarks. In addition, when there is distortion of the lateral ventricles caused by intracranial pathology, ventricular catheter placement ecomes even more difficult.

209.3.4.2 Transducer-Tipped Catheters

Transducer-tipped catheters are a newer class of ICP monitoring devices. The primary pressure transducer is mounted on the distal tip of the implanted catheter. Because the transducer is intracranial, these devices do not require leveling. Both fiberoptic and electrical sensors (miniature strain gauge type) are used in these monitoring systems.[4] 884 885

Fiberoptic pressure sensing methods include intensity modulation and interferometry. A mechanical diaphragm moves with changes in pressure in both methods and a monitor displays the corresponding ICP value. In the case of intensity modulation, the position of the diaphragm alters the intensity of the light reflected from its rear surface; with the interferometer, the position of the diaphragm is sensed by measuring the ratio of returned light intensities in two spectral bandwidths. This ratio is a function of spectral interference that varies with the position of the diaphragm. Fiberoptic transducers can record pressures from the intraventricular, intraparenchymal, subarachnoid and/or subdural compartments of the brain.[2,3]

Fiberoptic ICP monitoring systems, developed for use in humans, have been effective for dogs and cats.[5] ICP can be measured from the CSF or brain parenchyma and is effective in monitoring changes in ICP under anesthesia and during intracranial surgery.[5]

Catheter tip strain gauge pressure sensing devices use a miniaturized silicon transducer enclosed in a titanium case and implanted in the tip of a flexible nylon catheter.[6] Changes in the position of the diaphragm cause changes in the electrical resistance that is recorded and displayed by interface with a control unit for continuous monitoring of ICP. The control unit may then be interfaced with a wide variety of standard patient monitoring systems for ICP values, waveform display, or for consolidation of data with other physiologic parameters being monitored. Catheter tip ICP sensors are versatile and may be placed in a ventricle, in brain parenchyma, or the subarachnoid, subdural and/or epidural spaces. This system has been used experimentally in awake and anesthetized normal dogs.[6] It has also been used successfully in anesthetized dogs during craniotomy procedures with continued monitoring in awake dogs for 2 to 5 days postoperatively. Placement of the sensor is technically easy and the system allows complete freedom of movement in awake animals.

209.3.4.3 Subarachnoid Bolt

The subarachnoid bolt is a metal tube or screw secured to the calvarium through a burr hole placed over a cerebral convexity. The tube, which opens into the subarachnoid space, allows for measurement of ICP via fluid coupling to an external pressure transducer or from a sensor placed intracranially into the subarachnoid space.[2,3]

209.3.4.4 Fluid-Filled Catheter

Epidural or subdural placement of a sensor or a simple fluid-filled catheter connected to an arterial pressure monitoring system is cost effective and serves the purpose of monitoring adequately. Although the accuracy of this system may be questionable, fluctuations and trends in ICP are generally reliable. Dewey et al reported the use of such a system in normal cats and found that it was a reliable alternative to the fiberoptic intraparenchymal monitoring system.[7]

Transcranial Doppler ultrasonography is a noninvasive method of assessing the state of the intracranial circulation and can indirectly predict ICP. It may be useful occasionally in young puppies or hydrocephalic dogs with fontanelles for measuring changes in cerebral vascular resistance.

209.4 EVALUATION OF INTRACRANIAL PRESSURE

209.4.1 Normal Intracranial Pressure

Normal ICP values reported in the dog and cat vary from 5 to 12 mm Hg above atmospheric pressure.[5,6] ICP is not a static state, but one that is influenced by several factors. When recording ICP, two types of phasic changes can normally be seen in the pressure tracing.[1,2] These fluctuations in ICP are the result of cyclic changes in cerebral blood volume caused by the cardiac and respiratory cycles.

- The CSF fluid pulse pressure wave is caused by contraction of the left ventricle of the heart with resulting distention of the arterioles. The ICP tracing is similar to that of the peripheral arterial blood pressure tracing, with a systolic rise followed by a diastolic fall and a dicrotic notch.
- The pulse pressure waves exhibit characteristic waveforms at faster graphing speed. Changes in the amplitude and shape of this waveform often provide an early indication of changes in ICP and brain compliance[1,2] (see Figure 209-2).
- The ICP respiratory waves are slower pressure oscillations that fall with inspiration and rise with expiration. They are produced by both fluctuations in arterial blood pressure and cerebral venous outflow that cause an overall fluctuation in cerebral blood volume and, consequently, ICP (Figure 209-2).

Various physiologic phenomena such as coughing, sneezing, straining, or a low head position can raise pressure dramatically in the brain secondary to increased central venous pressure and the resulting retrograde transmission to the CSF.[2,6] In a normal animal, the intracranial tissues are compliant, and such intermittent elevations in ICP are transient and go unnoticed clinically. In animals with intracranial pathology and preexisting ICH, ICP may increase precipitously and may stay that way. Similarly, ICP can be affected by maneuvers such as compression of the jugular veins, suctioning the back of the throat, and regurgitation.

An absolute level wherein ICP is considered pathologically elevated has not been established in humans or animals. Treatment of ICH generally is recommended in humans for ICP measurements greater than 15 to 20 mm Hg. Because adequate CPP is more important than ICP per se, giving 885 886 an exact value whereby treatment is initiated in an animal is not possible until studies, using similar monitoring systems, are done on larger numbers of animals with similar disease processes. General trends in ICP, as well as significant, sustained changes in CPP, may be as useful to guiding therapy and prognosis as the specific ICP measurement that is recorded. In patients that have not been anesthetized, ICP monitoring is used in combination with meticulous and ongoing visual assessment of the patient to guide treatment decisions for animals with ICH. ICPs of 25 to 40 mm Hg, with adequately maintained CPPs, are seen routinely in severely brain-injured animals that subsequently fully recover.[5,6] In anesthetized or comatose patients, treatment of ICH should be considered when ICP values are 15 to 20 mm Hg and slowly increasing, when ICP values are lower than 15 mm Hg but rapidly increasing, or when CPP is not being maintained adequately.

209.4.2 Accuracy of Intracranial Pressure Monitoring Systems

In human medicine, with defined limits of treatment of ICH (i.e., 15 to 20 mm Hg), there is considerable discussion on the accuracy of ICP monitoring technology; clinicians worry that ICP may be underestimated or overestimated and therefore they may either incorrectly treat or not treat patients. Although treatment standards have not been so well defined in veterinary medicine, the user must have an understanding of the limitations of the device being used. In addition, compartmentalization within the cranium, zero drift (with catheter tip transducers), and leveling to obtain accurate measurements (with external transducers) must be taken into account.[4] In particular, fluid-filled systems may have inaccuracies from leakage in stopcocks, improper positioning in the CSF space, and occlusion with debris.[3,7]

Although ventricular pressure measurement is still considered the gold standard for accuracy in monitoring ICP, catheter tip pressure transducers have a similar accuracy. Many studies have been done looking at the phenomenon of compartmentalization in the brain. ICPs can vary within and between the intracranial compartments: brain and CSF, supratentorial versus infratentorial location, and within and between hemispheres.[3] In addition, because the contents are not homologous due to variation in tissue and capillary density, pressures may vary throughout the brain even without pathology.

In human studies, ICP is assessed most accurately by monitoring the cerebral hemisphere ipsilateral to the lesion.[3] Surface ICP monitors, such as epidural and subdural catheters and bolts, generally are considered less accurate than ventricular catheters or intraparenchymal devices, because they are not necessarily reflective of events occurring deep within the brain.[2] In a study monitoring ICP in seven normal dogs using catheter tip strain gauge transducers, no significant difference in ICP was recorded within or between cerebral hemispheres when multiple recordings were taken simultaneously in anesthetized and awake dogs.[6]

209.4.3 Complications of Intracranial Pressure Monitoring

Complications are rare overall and should not be used as a deterrent in deciding to use an ICP monitor if it is indicated.[4] The most common complications reported in humans include infection, hemorrhage, malfunction, obstruction, and malposition.[2-4] Infection and hemorrhage are associated more commonly with intraventricular catheter placement, and malfunction (obstruction, breakage) may be more common with catheter-tipped devices.

209.4.4 Indications for Intracranial Pressure Monitoring in Dogs and Cats

The correlation between elevated ICP and a poorer outcome in patients with severe brain injury has been shown in many human studies. Lowering elevated ICP ensures adequate CPP, reduces the risk of herniation, and optimizes recovery. Because placing an ICP monitor is associated with a small risk of complications as well as added cost, it is reasonable to limit its use to patients that are at most risk of herniation from ICH. ICP monitoring of brain-injured animals is likely to be most useful in the following situations:

1. Animals that are anesthetized or comatose, including animals undergoing and/or recovering from intracranial surgery

2. Animals with severe, progressive neurologic deterioration that may respond to a specific therapy with time, such as intracranial infection or inflammatory brain disease

3 Severely and traumatically head-injured patients

4 Research animals

209.5 SUGGESTED FURTHER READING*

RS Bagley: Options for diagnostic testing in animals with neurologic disease. In RS Bagley (Ed.): *Fundamentals of veterinary clinical neurology*. ed 1, 2005, Blackwell Publishing, Oxford, *Chapter that provides a synopsis of most of what has been published on ICP monitoring in dogs and cats and also summarizes most of the work that has been done using the Camino ICP monitor in dogs and cats*.

AM Marmarou, A Beaumont: Physiology of the cerebrospinal fluid and intracranial pressure. In HR Winn, JR Youmans (Eds.): *Youmans neurological surgery*. ed 5, 2004, Saunders, Oxford, *The human neurosurgeon's "bible" on general intracranial physiology*.

BK Sturges, RA LeCouteur, LD Tripp: Intracranial pressure monitoring in clinically normal dogs using the Codman ICP Express and Codman Microsensor ICP transducer. In 18th ACVIM Annual Veterinary Medical Forum, Seattle, WA 2000, *Summarizes the use of the miniature strain gauge transducer (Codman ICP monitoring system) in normal dogs*.

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* See the CD-ROM for a complete list of references

210 Chapter 210 Sedation Monitoring

Laurie Sorrell-Raschi, DVM, DACVA

210.1 KEY POINTS

- Sedation is the practice of delivering sedative and/or analgesic drugs to patients for procedures in which general anesthesia is considered unwarranted or undesirable.
- Because respiratory and cardiovascular depression may result following sedative or analgesic drug administration, the clinician should always be prepared to give the patient ventilatory and cardiovascular support.
- All sedated patients should receive supplemental oxygen.
- The minimum standard of sedation monitoring is vigilance.
- Continuous electrocardiographic and blood pressure monitoring, as well as capnography of the sedated patient, is valuable.
- Pulse oximetry is one of the most useful monitoring tools for the sedated patient.
- Level of consciousness must be monitored closely in all sedated patients.
- If the animal needs to be unconscious during the procedure, general anesthesia should be considered.

210.2 INTRODUCTION

Sedation can be defined as a chemically induced state of ease, or extreme calm and well-being. In such a state a patient is capable of responding to his surroundings but is unafraid and calm. Ideally, sedation should be achieved with minimal change in the patient's level of consciousness, produce few adverse cardiovascular and respiratory effects, and require minimal monitoring. In clinical practice, however, sedative drugs rarely are given merely for their calming effects. In modern veterinary medicine, sedation is evolving as a method of performing procedures that are too long, stressful, and/or painful for the patient to undergo without the benefit of some form of hypnotic, anxiolytic, and/or analgesic agent. Because no single drug is generally capable of providing all of those things, sedation strategies often rely on combinations of drugs to provide appropriate levels of relaxation. This increases the likelihood of undesirable side effects such as cardiovascular and respiratory depression.

In human medicine, the term *conscious sedation* was derived to describe the practice of delivering sedative and/or analgesic drugs to patients for procedures in which general anesthesia is considered unwarranted or undesirable. This method relies heavily on the human ability communicate. The principle is a simple one: the greatest danger with sedation is that as sedative levels deepen, the patient becomes more likely to lose consciousness, lose control of the gag reflex, and suffer from cardiovascular and respiratory depression. In humans, loss of verbal responsiveness is an early indicator that sedation has become too deep and the transition from sedation to anesthesia has occurred. Because most veterinary species are nonverbal, it is important to watch for less overt signs of patient stability. When progressively deeper levels of sedation are required, careful monitoring is essential. The level of monitoring necessary to ensure patient safety will depend on the patients status and the drugs and dosages employed to produce the required level of sedation.

210.3 BEFORE GETTING STARTED

Before any means of chemical restraint or sedation is employed, it is important to keep in mind that although many of the drugs used in sedation protocols cause minimal change in mentation or depression of the cardiovascular and/or respiratory system by themselves, few of these drugs are used alone. There are two rules of thumb: (1) the drugs that work best alone are those most likely to have adverse affects on their own (e.g., α_2-agonists, propofol) and (2) drugs may cause more adverse respiratory and cardiovascular effects when given together than any of them demonstrates when given alone.

Respiratory depression is one of the more common adverse sequelae of sedation.[1] It is therefore advisable to have supplemental oxygen available whenever sedative drugs are administered. Oxygen via a face mask is benign and well tolerated by most sedated dogs and cats. It is also recommended that emergency airway supplies are nearby (e.g., endotracheal tubes, laryngoscope and blade, Ambu bag) should intubation become necessary (see Chapter 17, Endotracheal Intubation).

210.4 DRUGS

See Chapter 162, Sedation of the Critically Ill Patient, for more information.

210.4.1 Tranquilizers

210.4.1.1 Phenothiazines

Acepromazine is the most commonly used drug in this class. It is a 2-acetyl derivative of promazine with a long duration of action (4 to 6 hours, however there have been some reports of effects as long as 12 hours). Many routes of administration can be employed (intramuscular [IM], intravenous [IV], subcutaneous [SC], or per os [PO]), but it has a slow onset of action (20 or more minutes) with all routes except IV (approximately 10 minutes).[2-5]

As with all phenothiazine tranquilizers, acepromazine acts within the central nervous system (CNS) to inhibit dopamine and 5-hydroxytryptamine receptors within the basal ganglia, limbic system, reticular activating system (RAS), hypothalamus, and brainstem. Acepromazine also exhibits antiemetic effects at the chemoreceptor trigger zone and vomiting center and has centrally mediated antihistamine-1 effects. It produces little respiratory or direct myocardial depression. There is experimental evidence that acepromazine may be protective against epinephrine-induced cardiac arrhythmias and may increase vagal tone.[3,6,7] It may cause peripheral α_1-receptor blockade in the vasculature, leading to peripheral vasodilation. Although this drug is generally well tolerated in stable, hydrated animals, it may lead to cardiovascular instability in more compromised patients.

210.4.1.2 Benzodiazepines

Benzodiazepines are multipurpose drugs used to provide not only tranquilization, but muscle relaxation, antiseizure activity, and anxiolysis (see Chapter 185, Benzodiazepines and Flumazenil). Benzodiazepines exert sedative and behavioral effects through actions on the limbic system and muscle relaxing effects through inhibition of internuncial neurons of the spinal cord. Benzodiazepines potentiate the actions of γ-aminobutyric acid (GABA), one of the two main inhibitory amino acid transmitters in the brain (glycine being the other). Diazepam and midazolam are the two most commonly used drugs in this category in veterinary medicine in the United States. Benzodiazepines produce minimal respiratory depression and very little cardiovascular depression. Midazolam may cause a greater decrease in blood pressure secondary to a decrease in systemic vascular resistance (SVR) compared with diazepam.[8] Although benzodiazepines by themselves produce little sedation in healthy dogs and cats, their utility lies in combination with other drugs. These drugs also have the added feature of reversibility (flumazenil).

210.4.2 Sedatives

210.4.2.1 α_2-Agonists

The α_2-agonists have potent sedative effects when administered by themselves.[9,10] α_2-Receptors are located throughout the spinal cord and brain and play a role in pain modulation as well as sympathetic outflow. When stimulated, α_2-receptors in the brain and spinal cord produce sedation and analgesia. α_2-Agonists may be given by many routes, including sublingual (SL). They are fast-acting drugs and their effects may be of short or long duration depending on individual drug pharmacokinetics (xylazine versus medetomidine). These drugs are also reversible with yohimbine or atipamezole, among others.

Unlike the tranquilizers previously mentioned, the cardiovascular effects of α_2-agonists can be profoundly negative. α_2-Receptors exist on the peripheral vasculature, as well as in the CNS. After the administration of an α_2-agonist these receptors are activated and cause an increase in peripheral vasoconstriction that can be severe, more so when the drug is given IV than IM or SC. This usually is followed by a reflex bradycardia that may be profound, particularly if the blood pressure is high. This may persist as the centrally mediated effects of the drug (namely decreased sympathetic outflow) occur, and hypotension may result.

Typically patients ventilate and oxygenate adequately, but respiratory side effects may occur. The mucous membranes appear pale, but this color change is often the result of vasoconstriction rather than poor ventilation or oxygenation; however, hypoventilation has been reported subsequent to α_2-agonist administration.[9]

210.4.2.2 Opioid Analgesics

Opioid drugs, like α_2-agonists, exert their effects through receptors (μ, κ, δ) that are located throughout the spinal cord and brain (see Chapter 184, Narcotic Agonists and Antagonists). Of these, the μ and κ receptors modulate analgesia and sedation.

Depending on the specific opiate chosen, dose and route of administration, opioids may produce a range of sedative effects from minimal to profound sedation. Paradoxically, like the benzodiazepines, opioids may also produce excitement rather than sedation in healthy alert animals, particularly cats.[4]

Opioid drugs are advantageous because they may be given by many routes (IV, IM, SC, PO), have a short or long duration of action, are cardiovascular sparing (although may increase vagal tone), provide analgesia, and are reversible (with naloxone).

The primary drawback to opioid drugs is that they may cause respiratory depression. This effect may be minimized by using butorphanol, a mixed μ-agonist-antagonist, or buprenorphine, a partial μ-agonist, both of which should have less respiratory depression effect than more selective μ-agonists.[2] Alternatively, respiratory depression may be reversed with an antagonist such as naloxone.

Although sedated patients undergoing procedures will ideally remain conscious with an intact gag reflex, it is important to keep in mind that opioid analgesics may also lead to decreased gastrointestinal motility and increased chance of vomiting. Whenever possible, patients should fast for an appropriate period before receiving opioid sedation, and general anesthesia with intubation should be considered in patients at high risk for vomiting or regurgitation and aspiration.

210.4.3 Dissociative Anesthetics

Ketamine is the most commonly used dissociative anesthetic in veterinary medicine.[11-13] Ketamine and other dissociative drugs disrupt the connection between the thalamoneocortical and limbic systems and depress the thalamoneocortical system. Patients usually breathe well, and although they may experience apneustic (short gasping breaths) respirations, they retain good laryngeal reflexes and continue to respond to their surroundings (may even have hypersensitive responses). Ketamine stimulates release of norepinephrine from adrenergic nerve terminals, thus indirectly augmenting sympathetic outflow. Generally ketamine helps maintain blood pressure; however, it has a direct negative inotropic effect on myocardial performance and may cause a decrease in blood pressure in critically ill patients. Ketamine may also cause muscle rigidity and seizures or hyperresponsive states when used alone in animals for chemical restraint.

Tiletamine is packaged in a fixed ratio with zolazepam as the drug Telazol. Because it is combined with a benzodiazepine, it has all of the advantages and disadvantages of both a dissociative drug and a benzodiazepine. Tiletamine, however, lasts much longer than ketamine (1 to 2 hours versus 15 to 20 minutes) and is more of a respiratory and cardiovascular depressant.

210.4.4 Propofol

Propofol is a sedative-hypnotic emulsion that induces CNS depression by enhancing the effects of GABA in the brain and decreasing the brain's metabolic activity. Propofol is administered IV and absorbed rapidly, providing quick loss of consciousness with a short duration, after a single bolus, in both dogs and cats. Propofol can be administered in combination with other drugs but also works well on its own. Propofol has a large volume of distribution and most likely some extrahepatic source of clearance, which allows for rapid recovery after a single injection. Sedation can be as short as 5 minutes following a single dose or as long as desired if repeated boluses or a continuous infusion is given. Infusions of longer than 1 hour may prolong the recovery time from propofol.[14]

Propofol may cause hypoventilation and hypotension secondary to peripheral vasodilation and myocardial depression when administered rapidly in dogs and cats.[13,15] In cats, propofol can also cause oxidative injury to red blood cells, producing Heinz bodies if it is given repeatedly over a period of hours to days.[16]

210.5 MONITORING

210.5.1 Basic

There are three main goals of monitoring patients during conscious sedation:

1. Monitor patient comfort and ensure that the animal tolerates the procedure.
2. Monitor the cardiopulmonary status. Ensure that the patient is ventilating and oxygenating well and is maintaining adequate perfusion.
3. Monitor the level of consciousness and ensure that the patient has not become anesthetized.

Whenever sedative procedures are performed, the minimum standard in monitoring is vigilance. Trained personnel should be on hand to observe the patient for signs of distress. If instrumentation is unavailable, ventilatory status may be evaluated by monitoring respiratory rate and effort. Mucous membrane color may give an indication as to the patient's oxygenation status (i.e., cyanosis may indicate hypoxia). Pulse rate, rhythm, and quality, mucous membrane color, and capillary refill time should be monitored to assess cardiovascular status. With deepening levels of sedation the palpebral reflex, patellar reflex, withdrawal to toe pinch, and reflex response to sound may be used to determine the patient's level of consciousness. Loss or severe blunting of one or more of these reflexes may indicate that the patient has made the transition from sedation to general anesthesia and may be in need of cardiovascular and/or ventilatory support.

210.5.2 Advanced

Although instrumentation should never be used as a substitute for trained personnel, it can be invaluable when monitoring a sedated patient, particularly those undergoing procedures that require deeper levels of sedation.

210.5.2.1 Electrocardiography

The electrocardiogram (ECG) is a means of continuously monitoring the electrical activity of the heart. Changes in rate, rhythm, or electrical configuration of the QRS complexes (ST segment depression and/or elevation) may give an early indication that the patient is in distress. One drawback to this monitoring device is that dogs and cats may object to application of the leads unless they are heavily sedated. Stick-on electrode pads may be more tolerable than alligator clips, especially in lightly sedated patients.

210.5.2.2 Noninvasive Blood Pressure Monitors

Multiple brands of monitors are available to measure blood pressure noninvasively in humans and animals. Most machines, employ one of three main methods: oscillometric, plethysmographic, or Doppler methods. All three techniques have their advantages and disadvantages depending on the species (cat or dog) and the circumstances in which they are used.[17-19] Regardless of the method, all of these techniques provide a more precise determination of blood pressure when used properly than does pulse palpation alone. Particularly in animals with deepening levels of sedation, it is advantageous to use some type of noninvasive blood pressure monitoring to assess the patient's cardiovascular status.

210.5.2.3 Capnometry

A capnometer monitors end-tidal carbon dioxide ($ETCO_2$) which, under normal circumstances (normal lung parenchyma, normal lung perfusion), is a reflection of arterial carbon dioxide (see Chapter 207, Capnography). It is, therefore, an indirect measure of effective ventilation. Although capnography is most effective when used on intubated patients, other techniques have been described for use in patients that are breathing spontaneously. Sidestream capnographs have been used in oxygen masks or in cannulae placed in the nares of more sedate patients, providing readings that correlate well with blood gas results in spontaneously breathing, nonpanting dogs.[20] The advantage of capnometry is that it may allow real-time monitoring of ventilatory status as well as perfusion.[21] Abrupt decreases in $ETCO_2$ can indicate a profound decrease in cardiac output, ventilation, or both. At the very least, such a decrease should warrant further investigation.

210.5.2.4 Pulse Oximetry

The pulse oximeter is used to noninvasively monitor arterial oxygen saturation (see Chapter 208, Blood Gas and Oximetry Monitoring). In humans undergoing anesthesia, the pulse oximeter is considered one of the most valuable monitoring tools. According to the American Society of Anesthesiologists (ASA) Committee on Professional Liability analysis of closed anesthesia claims, adverse respiratory events occurred more frequently than any other outcome claimed and probably could have been detected if a pulse oximeter had been employed.[1,22] As a result of this study and others, pulse oximetry is now considered part of the ASA standard of monitored sedation care.

Although dogs and cats have a high tolerance for the respiratory depressant effects of opioids, sedation of animals always carries the risk of respiratory depression. Pulse oximetry is a useful tool because it is noninvasive, easy to apply, and generally well tolerated. It also has the advantage of providing information about cardiovascular status. Because the pulse oximeter must detect a pulse signal to function, changes in the quality of the pulse signal may alert the clinician to changes in perfusion when more cumbersome monitoring equipment is not available or not tolerated by the patient.

210.5.2.5 Temperature

With deeper levels of sedation the patient's body temperature should be monitored every 15 minutes, as 889
tolerated by the patient. Many drugs used for sedation (e.g., phenothiazines, α_2-agonists) may disrupt 890
thermoregulation. Smaller patients such as cats and small dogs will be more likely to cool with deeper levels of sedation than larger ones because of their low body mass–to–surface ratios. Shivering will increase oxygen consumption and may predispose the patient to hypoxia if supplemental oxygen is not employed.[23] Every attempt should be made to keep the patient within 2° to 3° F of normal body temperature while sedated.

210.5.2.6 Monitoring the Level of Consciousness

Conscious sedation was developed in humans as a means of accomplishing two tasks:

1. Providing comfort and analgesia for people during procedures that were too painful to be done without chemical support, but did not warrant general anesthesia

2 To provide an alternative method of performing procedures on patients who were considered too high risk for general anesthesia

In veterinary medicine, sedation has evolved similarly. However, veterinary medicine differs from human medicine inasmuch as most veterinary patients are nonverbal. One of the main difficulties inherent in sedating animals is that there are no clear guidelines as to what constitutes sedation. Even in human literature there is little agreement as to what distinguishes light from mild, moderate, or deep sedation. What is agreed upon, however, is that as the patient's level of sedation gets deeper, laryngeal, ventilatory, and cardiovascular function are more likely to be compromised.

It is of paramount importance that the patient's level of consciousness be monitored. In human medicine, the level of consciousness is monitored continuously by assessing a patient's response to verbal and tactile stimuli.[1] As this is not possible in veterinary patients, it is generally assumed that the patient is comfortable if there is no voluntary movement, and this lack of movement is often used as the end-point of drug administration.

However, even at the deepest level of sedation, the patient should maintain a palpebral reflex and respond to verbal or tactile stimuli such as a toe pinch withdrawal or involuntary reflexes such as the patellar reflex (if the patient is sedated appropriately and the clinician is careful, one or more of these reflexes can be assessed without unduly disturbing the patient during the procedure). If the patient will not remain still enough to allow the procedure to be performed at this level of consciousness, then it is likely more prudent to perform the procedure under general anesthesia.

210.6 CONCLUSION

Conscious sedation is a useful procedure to allow various diagnostic, medical, and surgical procedures to be performed when general anesthesia is unavailable, too dangerous, or unwarranted. It is a valuable tool to the practicing veterinarian; however, it must be used appropriately to be performed safely. All sedated patients should be monitored for ventilatory and cardiovascular stability and their level of consciousness should be observed. Sedation should never be performed without careful consideration of the patient's needs during the procedure.

The veterinarian should not think of sedation as the quicker, safer alternative to general anesthesia. Too often clinicians choose to perform sedation rather than general anesthesia, thinking that sedation will be quicker, use less medication, cause less cardiovascular compromise, obviate the need for intubation, and provide for a quicker recovery. However, procedures may last for an extended period (requiring multiple bolus doses of sedative drugs), during which time the patients are actually unconscious with unprotected airways. Under these circumstances, none of the actual benefits of sedation exist, and general anesthesia would be a better and safer choice.

210.7 SUGGESTED FURTHER READING*

SH Binns, DD Sisson, DA Buoscio, DJ Schaeffer: Doppler ultrasonographic, oscillometric sphygmomanometric, and photoplethysmographic techniques for noninvasive blood pressure measurement in anesthetized cats. *J Vet Med.* **9**, 1995, 405, *A good comparative study that found the oscillometric technique to be the least accurate and least efficient of the tested methods; underestimated blood pressure in cats by increasing amounts as the blood pressure increased.*

DA Grosenbaugh, WW Muir: Blood pressure monitoring, symposium. *Vet Med.* **93**, 1998, 48, *An excellent review of basic blood pressure monitoring techniques in small animals.*

JC Hendricks, LG King: Practicality, usefulness and limits of end-tidal carbon dioxide monitoring in critical small animal patients. *J Vet Emerg Crit Care*. **4**, 1994, 29, *One of the only studies that uses an* $ETCO_2$ *monitoring technique in awake animals. A well-executed study whose authors discuss its limitations and provide valuable insight into the use of* $ETCO_2$ *monitoring in small animal medicine*.

CH Simon: Monitored anesthesia care. In PG Barash, BF Cullen, RK Stoelting (Eds.): *Clinical anesthesia*. ed 4, 2001, Lippincott Williams & Wilkins, Philadelphia, *One of the primary anesthesia texts used in human medicine. A well-referenced textbook chapter*.

JC Thurmon, WJ Tranquilli, GJ Benson: Preanesthetics and anesthetic adjuncts. In JC Thurmon, WJ Tranquilli, GJ Benson (Eds.): *Lumb and Jones' veterinary anesthesia*. ed 3, 1996, Williams & Wilkins, Baltimore, *A commonly referenced anesthesia text for veterinarians at all levels*.

* See the CD-ROM for a complete list of references

211 Chapter 211 Electrocardiogram Evaluation

Matthew S. Mellema, DVM, PhD

211.1 KEY POINTS

- The electrocardiogram (ECG) is an extremely useful and cost-effective monitoring tool.
- ECG monitoring is indicated for nearly all critically ill patients.
- Rather than a limited study of multiple leads, continuous monitoring of a single lead is the basis of most ECG monitoring in the critically ill patient.
- ECG interpretation should be systematic and thorough to gain the most benefit from its use.
- Trends in ECG alterations may alert the clinician to changes in the patient's condition even when the absolute values of those parameters still fall within the normal ranges.
- Electrolyte abnormalities, hypoxemia, effusions, and pain may cause acute detectable ECG changes without necessarily altering the underlying rhythm.

211.2 INTRODUCTION

Disorders of cardiac rhythm and conduction are encountered frequently in critically ill veterinary patients. Arrhythmias may be encountered in patients with primary cardiac disease or may be one manifestation of systemic illness. The severity of rhythm and conduction disturbances can range from inconsequential to acutely life threatening and can progress rapidly from one extreme to the other in some patients.

The electrocardiogram (ECG) is the diagnostic and monitoring tool used to confirm, detect, and define cardiac conduction and rhythm disturbances. In addition, the ECG provides the clinician with continuous real-time data regarding the patient's heart rate and rhythm, which can be informative even in the absence of gross abnormalities. This chapter will focus on the use of the ECG as a monitoring tool. For details of the recognition and treatment of specific cardiac rhythm disorders the reader is referred to other sections of this book (see Chapters 45 to 47, Bradyarrhythmias and Conduction Abnormalities, Supraventricular Tachycardia, and Ventricular Tachyarrhythmias, respectively).

211.3 INDICATIONS

The ECG is an extraordinarily cost-effective and useful monitoring tool. In veterinary intensive care the ECG may be second only to serial, well-performed physical examinations in terms of its usefulness in overall patient monitoring. Although a brief multiple lead evaluation of a patient's ECG is an important part of any diagnostic workup of suspected intrathoracic disease, in the intensive care setting continuous monitoring of cardiac rate and rhythm (typically one or a few leads at a time) is of greatest utility.

Some might argue that all critically ill animals warrant continuous ECG monitoring, and such statements may be true. However, some patients may have conditions that preclude continuous ECG monitoring and may instead mandate that intermittent evaluations be performed instead. One example of such a patient is a dog with central nervous system disease that is exhibiting circling. In this patient's case, ECG lead wires may represent a significant tangling or tripping hazard to the patient. Also, patients with diffuse dermatologic disease may not tolerate typical lead placement. With such exceptions in mind, one can state that most critically ill patients may benefit from continuous ECG monitoring. In particular, any patient with an irregular rhythm, increased heart rate, or decreased heart rate detected on physical examination should have ECG monitoring.

211.4 ELECTROCARDIOGRAPHIC PRINCIPLES

During depolarization and repolarization of the myocardium, the heart generates an electrical field that can be detected at the surface of the body by ECG leads. The system used in clinical practice consists of a series of positive and negative leads that when placed around the heart (roughly in the frontal plane either on the trunk or the limbs) will record complexes associated with the various phases of the cardiac electrical cycle. The ECG detects the sum of all the electrical impulses generated by the individual myocytes during each cycle. When a positive deflection is seen on the ECG tracing it signifies that the sum of the heart's electrical impulses was moving toward the positive electrode of that lead. A negative deflection signifies that the sum of the impulse was moving away from the positive electrode at that time. Impulses traveling perpendicular to an electrode do not cause a deflection in the tracing. When these deflections are plotted over time, a series of waveforms (P, QRS, and T) are detected.

The standard leads used in veterinary practice include the three bipolar leads (I, II, and III) and the augmented leads (aVR, aVL, and aVF). Each lead can produce a tracing of the heart's electrical activity from a different angle. In combination, the information obtained from multiple leads can aid in the diagnosis of rhythm and conduction disturbances. When measurements of the P-QRS-T waveforms are performed, these should be done using a lead II tracing.

211.5 TECHNIQUE

Many lead attachment systems are available. When selecting a system it is important to bear in mind that high-quality ECG recordings require good contact between the leads and the patient's skin. If commercially available self-adhesive lead pads are to be used, then it is advised that the hair be clipped and the skin cleaned and dried before application. Generally, lead pads placed over the lateral thorax on each side and a third pad in the left inguinal region is sufficient to obtain good quality tracings. Alligator clips are not advised for continuous monitoring, because their prolonged use can damage the patient's skin and cause discomfort. Once the lead pads are placed and lead wires attached, it is often helpful to place a mesh stockinette shirt around the patient's trunk so that all leads can be collected into a single “stalk” exiting the mesh shirt dorsally. This can enhance patient comfort, prevent lead detachment, and reduce obstacles to patient repositioning.

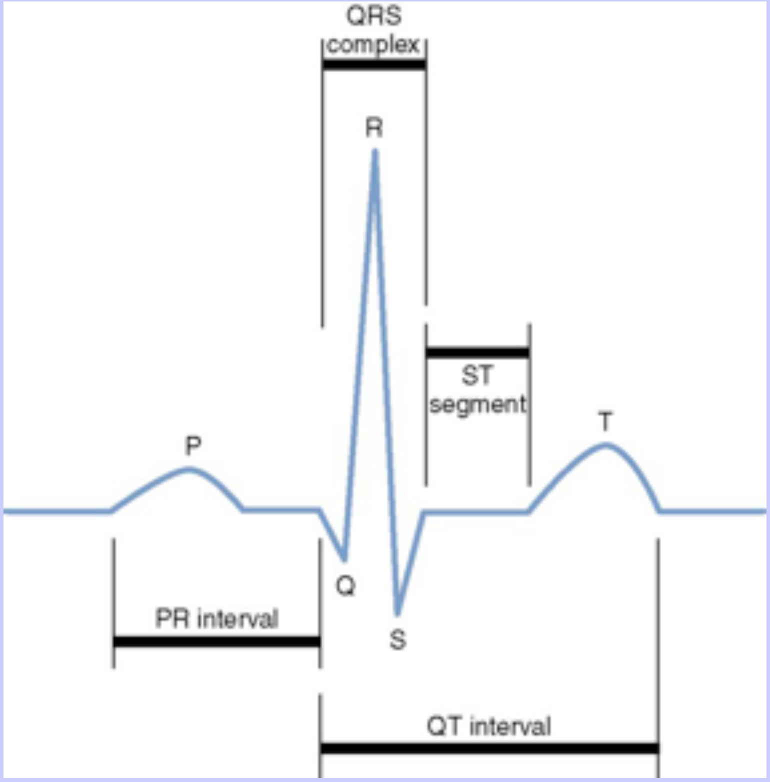
When selecting a lead to display during continuous ECG monitoring one should select the one that the caregiver believes provides the most easily recognizable waveforms. Lead II is used for rhythm evaluation in cardiac examinations, because in most patients this lead lies well within the mean electrical axis of the heart and will produce easily recognizable waveforms. However, in the critically ill patient the caregiver may need to evaluate several leads to find the one which gives the most robust signal.

If one is relying on the monitor to calculate heart rates automatically, one will often get more accurate readings if a lead is picked in which the QRS amplitude is markedly different from that of the P and T waves (otherwise double or triple counting may occur, giving erroneously high heart rate readings). It should always be noted in the patient's record which lead is being monitored. It is essential that the clinician and nursing staff bear in mind that the normal values for canine and feline ECGs are obtained from still animals in right lateral recumbency. During continuous monitoring the patients are seldom, if ever, in the ideal position and changes in waveform amplitude are to be expected relative to normal values. The utility of the continuous ECG is predominantly in monitoring heart rate and rhythm; however, it can also alert the clinician as to whether a standardized recording of all six leads and a rhythm strip should be performed.

211.6 ELECTROCARDIOGRAM WAVEFORMS

Figure 211-1 shows a normal canine lead II P-QRS-T complex with the waveforms, intervals, and ST segment identified. The P wave is a reflection of the depolarization of the atria. Its duration and amplitude should be noted. The PR interval is measured from the beginning of the P wave to the start of the QRS complex and is a measure of the time it took for the electrical impulse to travel from the sinoatrial node to the ventricular myocardium (including the normal delay that occurs as the impulse travels through the atrioventricular node). The QRS complex is a reflection of ventricular depolarization. As with the P wave, the duration and amplitude of the QRS complex should be evaluated. The ST segment is measured from the end of the QRS complex to the beginning of the T wave. Disease states can cause the ST segment to be shifted upward or downward from the baseline, and any such shifts should be noted. The T wave is the result of ventricular repolarization. Although the shape and amplitude of the T wave can be extremely variable in normal dogs, progressive or acute changes in the conformation of the T wave of an individual patient can be a marker of important disease states such as hypoxemia. The QT interval is an indicator of the time required for ventricular contraction to occur. This interval is measured from the start of the QRS complex to the end of the T wave. The duration of the QT interval can be an important indicator of electrolyte abnormalities.

Figure 211-1 Component waveforms, segments, and intervals of the normal electrocardiogram.



211.7 ELECTROCARDIOGRAM INTERPRETATION

The most important principle in ECG interpretation is that each ECG should be evaluated in the same systematic way. Any thorough evaluation should include the following:

1. Calculation of heart rate
2. Determination of the rhythm
3. Identification of the waveforms (P-QRS-T) with particular attention paid to changes relative to previous evaluations of this same patient
4. Evaluation of the PR and QT intervals
5. Inspection of the ST segment for elevation or depression

Each of the above should be compared with normal values (Table 211-1) and to previous measurements made from this same patient. Serial evaluation can provide important early indications of changes in the patient's condition, even when values fall within the normal range. For example, progressive elongation of the QT interval or QRS duration may signal worsening hyperkalemia in a patient long before the absolute values of these measurements leave the accepted normal range. Care must be taken when evaluating the amplitude or orientation of the waveforms relative to normal values if they were not obtained from a still animal in right lateral recumbency (as the normal values were). Changes in the durations of the intervals and waveforms seldom are affected by patient position, whereas the orientation and amplitude of the waveforms can vary markedly. 892

Table 211-1 Normal Canine and Feline Lead II Electrocardiogram Values

	Canine	**Feline**
Heart rate	Puppy: 70 to 220 beats/min Toy breeds: 70 to 180 beats/min Standard: 70 to 160 beats/min Giant breeds: 60 to 140 beats/min	120 to 240 beats/min
Rhythm	Sinus rhythm Sinus arrhythmia Wandering pacemaker	Sinus rhythm
P Wave		
Amplitude	Maximum: 0.4 mV	Maximum: 0.02 mV
Duration	Maximum: 0.04 sec (giant breeds 0.05 sec)	Maximum: 0.04 sec
PR Interval	0.06 to 0.13 sec	0.05 to 0.09 sec
QRS		
Amplitude	Small breeds: 2.5 mV Large breeds: 3 mV	Maximum: 0.9 mV
Duration	Small breeds: 0.05 sec maximum Large breeds: 0.06 sec maximum	Maximum: 0.04 sec
ST Segment		
Depression	No more than 0.2 mV	None
Elevation	No more than 0.15 mV	None
QT Interval	0.15 to 0.25 sec at normal heart rate	0.12 to 0.18 sec at normal heart rate
T Wave	May be positive, negative, or biphasic Not more than one fourth of R wave amplitude	Usually positive

Modified from Tilley LP, Goodwin J, editors: *Manual of canine and feline cardiology,* ed 3, Philadelphia, 2001, WB Saunders.

211.8 EFFECTS OF DISEASE STATES ON THE ELECTROCARDIOGRAM

Specific arrhythmias and their management are discussed elsewhere in this book (see Chapters 45 to 47, Bradyarrhythmias and Conduction Abnormalities, Supraventricular Tachycardia, and Ventricular Abnormalities respectively). However, many disease states can produce detectable changes in the ECG before they become so severe that they alter the rhythm or shift the heart rate outside the normal range.

211.8.1 Electrolyte Abnormalities

The normal action potentials generated by both contractile and noncontractile cardiac cells are dependent on the sequential opening of a multitude of ion channels and the flow of ionized sodium, potassium, and calcium through these channels across the cell membranes. Further, other electrolytes such as magnesium serve as important cofactors in cellular actions relying on adenosine triphosphate, such as the function of cellular pumps that reestablish resting membrane potential after a depolarization. Thus it is not surprising that alterations in electrolyte concentrations can cause alterations in cardiac electrical and mechanical functions.

211.8.1.1 Hyperkalemia

Although most critically ill patients are faced with large ongoing potassium losses, a subset of animals may arrive with or develop elevated extracellular potassium levels. Such hyperkalemia may occur either as a result of the underlying disease process (e.g., Addison's disease), as a result of treatment (e.g., lysis of a saddle thrombus with subsequent reperfusion), or because of inadvertent administration of excess parenteral potassium ion (e.g., poorly mixed fluids supplemented with potassium chloride). Regardless of the etiology, the ECG can serve as an invaluable tool in the detection of hyperkalemia. As serum potassium levels rise above 5.5 mEq/L, the ECG may begin to show tall peaked T waves. As potassium levels rise to 8 to 9 mEq/L, QRS duration may become prolonged and P wave amplitude may diminish. With further increases in potassium, the QRS waves may take on a sinusoidal appearance, P waves may no longer be apparent, and ST segment elevation or depression may be noted.

211.8.1.2 Hypokalemia

Low serum potassium levels are a common finding in the critically ill patient and frequently need to be addressed when a fluid plan is formulated. When hypokalemia develops it may result in nonspecific ECG changes such as prolongation of the QT interval, reduced T wave amplitude, and ST segment depression. Severe hypokalemia may lead to both atrial and ventricular tachyarrhythmias.

211.8.1.3 Hypercalcemia

Similar to how they handle potassium, most sick and injured animals struggle to maintain a normal serum ionized calcium level. However, hypercalcemia may occur, resulting from either a primary disease state or administration of intravenous calcium preparations, or both; the elevation of this ion may be reflected by changes in the ECG. The most notable of these changes is QT interval shortening, and this finding can be an important signal to the clinician to measure both total and ionized calcium levels.

211.8.1.4 Hypocalcemia

As one might expect, the effects of hypocalcemia on the ECG are in direct contrast to those caused by hypercalcemia. Prolongation of the QT interval may be an indication of reduced serum calcium concentrations. Nonspecific changes in the shape of the T wave may be noted as well.

211.8.1.5 Magnesium

In humans, hypermagnesemia may cause prolonged PR intervals and QRS durations. Little is known about elevated magnesium levels in critically ill dogs and cats, although hypomagnesemia is a recognized condition occurring in a significant number of critically ill veterinary patients. Low magnesium levels cause ECG changes quite similar to those noted for hypokalemia.

211.8.2 Hypoxemia

Low partial pressure of arterial oxygen has a profound effect on cardiac function, sympathetic nervous system activation and, not surprisingly, the ECG. Severe or prolonged hypoxemia can produce both tachyarrhythmias and bradyarrhythmias and may lead to cardiac arrhythmias. However, in many patients the ECG can also provide early warning signs of worsening tissue oxygenation. Myocardial hypoxia may be reflected by elevation or depression of the ST segment. The sudden appearance of large T waves can herald hypoxemia, although any abrupt change in T wave appearance warrants an evaluation of the patient's blood gases.

211.8.3 Intrathoracic Effusions

The accumulation of effusions (or tissues as may be seen with diaphragmatic hernias) within the pericardial or pleural spaces can result in dampening of the ECG waveforms. Diminished or variable amplitude of the QRS complex should prompt the clinician to pursue further diagnostic measures to rule out intracavitary effusions.

211.8.4 Pain

Patient discomfort can lead to nonspecific alterations in the ECG. A progressively increasing heart rate with or without changes in T wave conformation can be a sign of increasing sympathetic nervous system output. When these changes are seen in a patient exhibiting other signs of discomfort, alleviation of pain may lead to normalization of the ECG parameters.

211.9 SUGGESTED FURTHER READING*

E Braunwald, DP Zipes, P Libby, R Bonow (Eds.): *Braunwald's heart disease: A textbook of cardiovascular medicine*. 2004, Saunders, Philadelphia, *One of the most widely used textbooks in human cardiology. Very detailed. An excellent reference book.*

P Darke, JD Bonagura, DF Kelly: In *Color atlas of veterinary cardiology*. 1996, Mosby-Wolfe, London, *A high-quality atlas containing full-color reproductions of ECGs, echocardiograms, radiographs, and pathology specimens*.

LP Tilley: In *Essentials of canine and feline electrocardiography*. ed 3, 1992, Lea & Febiger, Philadelphia, *An excellent resource that covers the interpretation of ECGs as well as the management of arrhythmias in dogs and cats. Also contains discussions of the pathophysiologic basis of common arrhythmias. An updated edition due out in late 2006*.

LP Tilley, et al.: In *Canine and feline cardiology*. ed 4, 2008, St. Louis, Saunders, *A very-easy-to-use and straightforward text. Updated extensively from the second edition*.

LP Tilley, MS Miller, FW Smith, Jr.: In *Canine and feline arrhythmias: Self-assessment*. 1993, Lea & Febiger, Philadelphia, *A high-quality collection of ECGs presented in a case-based format that allows for self-paced learning and practice. Highly recommended*.

* See the CD-ROM for a complete list of references

212 Chapter 212 Cardiac Output Monitoring

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212.1 KEY POINTS

- Cardiac output is the volume of blood transferred by the heart to the systemic circulation over time.
- It is a key determinant of oxygen delivery and an early indicator of hemodynamic instability.
- Cardiac output should be measured in any patient wherein appropriate clinical decisions cannot be made without this information.
- Both invasive and minimally invasive methods of cardiac output measurement are available for clinical use in dogs and cats.
- Disease states can have a profound and complex impact on cardiac output.
- Complications of pulmonary artery catheters are rare, but placement should be done either by, or under the supervision of, experienced personnel.

212.2 INTRODUCTION

Delivery of oxygen to the body and the removal of cellular metabolic waste are the fundamental roles of the cardiovascular and pulmonary systems. To accomplish these vital functions the pulmonary and cardiovascular systems must work in concert in a complex yet deeply integrated fashion. Each system relies on a pumping mechanism to accomplish the transport of blood or respiratory gases to the sites where the exchange of substrates and waste occurs.

In the case of the cardiovascular system, the heart provides the pumping force and the blood vessels serve to conduct and distribute the pumped blood to the tissues. The elastic properties of the vascular tree allow the force generated by the heart to be stored and applied to the column of flowing blood throughout the cardiac cycle. The volume of blood transferred to the systemic circulation over time is termed *cardiac output*. Cardiac output in man is typically measured in liters per minute (L/min). Veterinary patients often come in a much broader range of shapes and sizes and, as such, cardiac output is often referenced in terms of milliliters of blood per kilogram body weight per minute (ml/kg/min). Normal values for dogs and cats typically range from 120 to 200 ml/kg/min.[1,2] A related measure is termed *cardiac index* and relates the volume of blood pumped over time to the animal's body surface area rather than body mass, because the former is thought to correlate with metabolic rate (the principal determinant of cardiac output). Cardiac index is expressed in liters per minute per square meters (L/min/m^2).[2]

Cardiac output is an important measure of cardiovascular function. It provides insights into the adequacy of blood delivery to the body as a whole. When taken together with measurements of the oxygen content of blood, it allows for the determination of whole body oxygen delivery.[1,2] If one knows the patient's heart rate, then knowledge of cardiac output allows the clinician to determine stroke volume. Cardiac output measurements also make it possible for the caregiver to determine important physiologic indicators such as intrapulmonary shunt, systemic and pulmonary vascular resistance, and oxygen consumption. This vast array of additional parameters that can be derived once cardiac output is known allow the clinician to make better informed decisions about the need for, or adequacy of, therapeutic interventions and to provide a detailed account of the patient's cardiovascular status.

212.3 INDICATIONS FOR CARDIAC OUTPUT MEASUREMENT

When performed by an experienced clinician, physical examination of the patient will reveal a great deal about the adequacy of oxygen delivery and cardiac output. Many of the findings of the physical examination relate directly to regional or organ-specific blood flow (e.g., capillary refill time, pulse pressure, mentation, urine production). Although these physical parameters are invaluable in the repeated assessment of patients and require little more equipment than a wristwatch, some are subjective measures and correlate poorly with an individual patient's actual cardiovascular status.[3] However, it must be noted that although an individual value for capillary refill time, for example, may correlate poorly with more direct measures of cardiac output, the trends in serial physical examination findings in an individual patient provide the best and most reliable measure of alterations in that patient's cardiovascular status. Unfortunately, the converse is not true: a patient whose physical examination findings are not changing may be experiencing a decline in cardiac performance that will not be detectable until compensatory mechanisms are exhausted or overcome.

The findings of a thorough physical examination, particularly when complemented with hemodynamic monitoring (see Chapter 203, Hemodynamic Monitoring), will be sufficient to guide the clinician in directing the care of most patients. However, there exists a subset of critically ill veterinary patients in whom more direct assessment of cardiac output (and its derived parameters) is essential to proper case management. Patients with sepsis, septic shock, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome make up the bulk of veterinary patients that are likely to require more invasive measures of cardiac output. Patients with severe compromise of the pulmonary or cardiovascular system may also require cardiac output monitoring to optimize their care. It is in the care of these patients that clinicians may find themselves unable to make appropriate decisions regarding management without the additional information provided via cardiac output monitoring.

In patients with complex disease states such as those mentioned above, the individual's cardiovascular and pulmonary systems may be compromised to such an extent that the typical measures of cardiovascular status and performance may give contradictory information and suggest therapies that have opposing mechanisms of action (e.g., expanding or depleting extracellular fluid volume). An all- too-common example is a septic patient that has developed capillary leak syndrome (enhanced permeability of systemic capillaries and venules, promoting tissue edema). This patient typically has a low central venous or mean arterial pressure, or both (suggesting additional intravenous fluid therapy would be of benefit), while at the same time exhibiting marked peripheral edema (which might lead the clinician to want to be less aggressive with fluid administration). The treatment of such a patient would be enhanced by the knowledge of the cardiac output and oxygen delivery, which are always of primary importance and can mandate a course of action in the face of conflicting findings. Cardiac output can also be a much earlier indicator of deteriorating cardiovascular status, because compensatory mechanisms such as reflex vasoconstriction can maintain other indicators such as mean arterial pressure near normal levels in the face of worsening cardiac performance.

212.4 MEASUREMENT OF CARDIAC OUTPUT

212.4.1 Invasive Methods of Determining Cardiac Output

All invasive techniques to measure cardiac output rely on one of two methods: the Fick oxygen consumption method or the indicator-dilution method. The commonly used thermodilution method is, in principle, a modification of the indicator-dilution method using thermal energy as the indicator. Both methods will be discussed.[4]

212.4.1.1 Fick Oxygen Consumption Method

This technique is considered the gold standard and is the oldest method for measuring cardiac output. The method relies on the Fick principle that states that the total uptake of (or release of) a substance by the peripheral tissues is equal to the product of the blood flow to the peripheral tissues and the arterial-venous concentration difference (gradient) of the substance. For a substance that is taken up by the tissues (such as oxygen), the Fick principle says "what went in minus what came out must equal what was left behind." The Fick principle when applied to cardiac output and oxygen uptake can be expressed as the following:

$$\text{Cardiac output} = \frac{\text{Oxygen consumption}}{\text{Arteriovenous oxygen content difference}}$$

When one uses the Fick method to determine cardiac output, oxygen consumption is determined by measuring the oxygen concentration difference in the inhaled air and the exhaled air collected from the patient over time (typically 3 minutes). The arteriovenous oxygen content difference is determined by measuring the oxygen content of both an arterial and a mixed venous blood sample. Although oxygen content analyzers are available, it is more typical for the clinician to measure the oxygen partial pressure (PO_2), hemoglobin saturation (SO_2), and hemoglobin concentration ([Hb]) with a blood gas analyzer and manually calculate oxygen content using the formula:

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$$\text{Oxygen content} = ([\text{Hb}] \times 1.36 \times SO_2) + (0.003 \times PO_2)$$

The principal drawbacks to this method in veterinary medicine are that it is not a continuous real-time measure of cardiac output and that reliable collection of respiratory gases requires that the patient be intubated. In addition, the Fick method relies on the patient maintaining a stable hemodynamic and metabolic state throughout the period of gas collection; thus the less stable the patient the less reliable this method becomes. Lastly, results obtained by the Fick method are invalid in the presence of significant intracardiac or intrapulmonary shunting of blood.

212.4.1.2 Indicator-Dilution Method (Including Thermodilution)

In actuality, the indicator-dilution method is simply an adaptation of the Fick method using indicators that are more easily collected and measured than elemental oxygen. The basis still lies in the Fick principle and conservation of matter (or thermal energy).

With this method an exogenous indicator is injected into the patient's mixed venous blood via a pulmonary artery catheter[5] (see Chapter 50, Pulmonary Artery Catheterization), and the dilution of the indicator is followed continuously until both the original concentration peak associated with injection and a secondary peak due to recirculation are observed. By plotting the concentration of the indicator against time, one can obtain the area under the curve of the concentration versus time plot. Cardiac output is determined by taking the known amount of indicator and dividing it by the area under the curve. Typically, this process is an integrated function of the software packages included with modern cardiac monitoring equipment. In the laboratory setting the indicator may be a dye such as indocyanine green; however, this method is seldom used in clinical patients.

The indicator of choice is thermal energy. Modern pulmonary artery catheters can be equipped with a sensitive thermocouple that can give highly accurate continuous measurements of blood temperature. This type of pulmonary artery catheter has been termed a *Swan-Ganz catheter* after the physicians who developed it and introduced it into clinical practice in human medicine.

Although the technology has advanced, the technique still relies on the Fick principle. By injecting a known volume of saline at a known temperature (typically room temperature; chilling is no longer needed with modern catheters) into the right-sided circulation, one can use the thermocouple to follow the dilution of this cool sample in the larger, warmer blood volume of the patient. Integration of this temperature signal can provide the clinician with a reliable measure of cardiac output. Recorded values are usually the average of three measurements taken in a short time, one after another. Good agreement is considered to be values that don't vary by more than 10%.

One difference in this method relative to other indicator-dilution techniques is that the indicator is injected into the right atrium and dilution is measured in the pulmonary artery. Dye dilution is performed by injecting into the pulmonary artery and measuring the dilution at an arterial site. The thermodilution method is by far the most widely used method in practice today and is at least as reliable as either of the two other methods discussed above.

Advances in ion-specific electrode technology have led to novel means of using indicator-dilution principles to determine cardiac output in humans and animals. One such advance is the development of an electrode for lithium ions that can be introduced into the patient's arterial bloodstream via an indwelling arterial catheter. Such an electrode can be used to record the dilution of small doses of lithium chloride injected into the venous circulation at either a peripheral or central site. Cardiac output determination by this method has been studied in both dogs and cats, and agreement with cardiac output values obtained via thermodilution methods has generally been good.[6,7] The lithium dilution method holds great promise because it does not require that a pulmonary artery catheter be in place. As clinical experience with the technique and evidence of the method's reliability grows, the lithium dilution method (or similar technology) may replace thermodilution as the method of choice for cardiac output determination in small animal practice.

212.4.2 Noninvasive Methods of Determining Cardiac Output

Although the lithium dilution method for determining cardiac output can be termed minimally invasive, it is not truly noninvasive because it requires placement of both venous and arterial catheters. For patients requiring long-term intensive care and cardiac output monitoring, the availability of patent peripheral arteries can become limited and limiting. Truly noninvasive methods of real-time continuous monitoring of cardiac output continue to be sought and will be discussed briefly here.

Transesophageal echocardiography has been used in man and a number of animal species as a minimally invasive means of tracking changes in cardiac output and performance. Measurement of blood velocity (using Doppler) and aortic diameter (using echocardiography) allow estimates of stroke volume to be obtained. To obtain truly reliable and quantifiable measurements of cardiac output, transesophageal echocardiography measurements should be initially (and periodically) calibrated against measurements obtained by one of the more invasive methods discussed above. The utility of this method is somewhat limited in small animal practice because of equipment limitations, the time required to obtain acceptable studies, patient tolerance of the probe, and the need for highly trained personnel to be on hand to make the measurements. However, it does hold promise in limited application (e.g., anesthetized patient evaluation and monitoring).

Thoracic electrical bioimpedance is a noninvasive method of evaluating changes in the conductivity of the thorax resulting from the pulsatile flow of blood within the thoracic cavity. Sets of electrodes similar to electrocardiogram electrodes are located superficially on the thorax. Although electrocardiogram electrodes simply measure voltage changes resulting from the intrinsic electrical activity of the heart, thoracic electrical bioimpedance utilizes electrodes that both measure and apply voltage. The principle is that by applying a small known voltage to the patient's thorax and then measuring what portion of that initial voltage reaches a distant sensing electrode, the conductivity (and impedance) of the thorax to flow of current can be determined. Changes in thoracic blood volume (blood and tissue are good conductors, air-filled lungs are not) can be detected, and estimates of stroke volume and cardiac output can be made using computer algorithms. Although this method holds promise in humans where the size and shape of the thorax is somewhat uniform, the variety of species and 896 897 breeds presented to the small animal clinician may make any single algorithm of limited utility, and estimates may require comparison with invasive methods with some frequency.

Analysis of the arterial pressure waveform is an additional form of algorithm-dependent monitoring that is minimally invasive (requires an indwelling arterial catheter). Changes in the conformation of the arterial pressure waveform can provide insights into alterations in the performance of the heart and the tone of the vascular tree. Although qualitative evaluation of arterial waveforms has been standard practice for decades, it is only fairly recently that efforts have been made to provide quantitative information from this source. One promising prospect is the use of lithium dilution methods to calibrate arterial waveform analyses, which may then provide continuous read-outs of cardiac performance. This is an active area of research in both humans and animals.

212.5 NORMAL VALUES

The normal values for cardiac output (and related and derived indexes) for dogs and cats are presented in Table 212-1. Values other than cardiac output and cardiac index are presented for the reader's consideration but are discussed in greater detail elsewhere (see Chapters 50, 64, and 203, Pulmonary Artery Catheterization, Daily Intravenous Fluid Therapy, and Hemodynamic Monitoring, respectively). The normal values presented in Table 212-1 represent composite values obtained from the literature and measurements made on clinical patients and research animals at the School of Veterinary Medicine at the University of California, Davis.[2] These composites include values from animals that were sedated, as well as lightly anesthetized animals. Values for fully awake animals might be considered true “normal” values but would not represent normal values for the setting in which clinical measurements are generally obtained.

212.6 POTENTIAL CAUSES OF ERROR

Any form of measurement of any parameter carries an intrinsic degree of error. It is the responsibility of the clinician and the nursing staff to avoid compounding this form of uncertainty by introducing additional sources of error (Table 212-2). To this end, clinicians seeking to measure cardiac output using any of the techniques discussed above should ensure that they have been trained by experienced personnel and have suitable “hands-on” experience with the method before using it in clinical decision making. Misuse of data from Swan-Ganz catheters by insufficiently trained personnel has on occasion led to iatrogenic injury and poor outcomes, and subsequently the devices have fallen out of favor in some segments of human medicine.

Table 212-1 Normal Cardiopulmonary Values for Dogs and Cats

Parameter (units)	Dog	Cat
Heart rate (min^{-1})	100 to 140	110 to 140
Mean arterial pressure (mmHg)	80 to 120	100 to 150
Cardiac output (ml/kg/min)	125 to 200	120
Cardiac index ($L/min/m^2$)	3.5 to 5.5	–
Stroke volume (ml/beat/kg)	40 to 60	–
Systemic vascular resistance (mmHg/ml/kg/min)	0.5 to 0.8	–
Mean pulmonary artery pressure (mm Hg)	10 to 20	–
Pulmonary vascular resistance (mmHg/ml/kg/min)	0.04 to 0.06	–
Central venous pressure (cm H_2O)	0 to 10	–
Pulmonary artery wedge pressure (mmHg)	5 to 12	–
Oxygen delivery (ml/kg/min)	20 to 35	–
Oxygen consumption (ml/kg/min)	4 to 11	3 to 8
Oxygen extraction (%)	20 to 30	–

All of the methods for measuring cardiac output that have been discussed rely on the patient having stable hemodynamics throughout the study period (typically several minutes). In the case of the Fick method, reliable measurements also require that the patient have only small fluctuations in metabolic rate during the study period. With each of the methods discussed, the serial evaluation of measurements is of greater use than any single measurement.

212.7 DISEASE STATES AND CARDIAC OUTPUT MEASUREMENT

Cardiac output is the product of stroke volume and heart rate. Disease processes that alter either of these factors may alter cardiac output (unless the disease affects both in opposite directions and to equal degrees). Decreasing heart rates may either improve or worsen cardiac output depending on the individual patient. Patients with stiff, noncompliant ventricles or tachyarrhythmias, for example, may benefit from a reduction in heart rate via greater filling during diastole. Alternatively, a patient with advanced atrioventricular node disease may have reduced cardiac output due to low (ventricular) heart rate.

Generally, any condition that reduces stroke volume will reduce cardiac output if heart rate changes are minimal. Stroke volume is determined by preload, afterload, and contractility. Preload is determined largely by cardiac compliance and filling pressures. Any disease state that reduces filling pressures (e.g., hemorrhage, dehydration) or 897 ventricular compliance (e.g., pericardial tamponade) can reduce 898 preload and cardiac output. Afterload is a complex determinant of stroke volume and is largely dependent on the tone of the vasculature (particularly arterioles), but in some patients is influenced by physical abnormalities in the vasculature (e.g., aortic stenosis, arteriovenous fistulas).

Table 212-2 Sources of Error in Cardiac Output Measurement (Thermodilution)

Error Source	Brief Description	Adjustments
Respiratory cycle	Pulmonary artery blood cools during inspiration Venous return varies with intrathoracic pressure	Make measurements at end expiration
Arrhythmias	Cause rapid and marked variations in stroke volume	Treat arrhythmias as indicated
Altered intracardiac flow	Shunting and regurgitation can cause some of the injectate to bypass the thermistor or delay arrival of some of the bolus volume	Thermodilution technique may be invalid in patients with significant flow abnormalities
Low cardiac output	Slow ejection causes warming of the injectate before it reaches the thermistor	Further therapeutic interventions will be required to increase cardiac output before values will be valid or repeatable
Injectate factors	Wrong solution, wrong volume, wrong temperature	Triple check all aspects of the bolus before injecting
Thermistor factors	Thrombus on the catheter tip Catheter migration Catheter defect	Check position and reposition or replace catheter as needed
Additional infusions	Simultaneous infusion of large volumes of crystalloid or colloid solutions can interfere with thermistor detection of the bolus	Either interrupt the fluid bolus or postpone cardiac output measurements as dictated by patient's needs

Any process that increases afterload may reduce cardiac output (e.g., α-adrenergic stimulation), and processes that reduce afterload (e.g., reduced blood viscosity, arteriolar dilation) may increase cardiac output. Contractility is a measure of the myocardium's ability to eject blood independent of preload. Contractility may, for example, be depressed by circulating mediators (e.g., sepsis, pancreatitis) or enhanced by β-adrenergic stimulation. Any alteration in a patient's cardiac output should prompt a careful consideration of how disease states may be altering heart rate, preload, afterload, and contractility. Factors known to adversely effect these determinants of cardiac output should be addressed whenever possible.

212.8 POTENTIAL COMPLICATIONS

The vast majority of patients in which cardiac output measurements are made experience no direct complications due to the instrumentation or procedures required. However, many complications can occur when hemodynamic data are misinterpreted, and this issue has been discussed earlier in this chapter. A small subset of patients in whom Swan-Ganz or other pulmonary artery catheters are placed will experience complications related to the placement, presence, or maintenance of the catheter.[8] These complications include, but are not limited to, the following: catheter-related sepsis, pulmonary artery rupture, damage to cardiac structures, catheter knotting (possibly requiring thoracotomy), hemorrhage, and embolization. For these reasons and others, it is stressed that pulmonary artery catheter placement is not a technique to be learned without the guidance of experienced personnel.

Complications from lithium chloride injection have not been reported in dogs or cats. The other methods of cardiac output determination discussed above also are considered to have a very large measure of safety.

212.9 SUGGESTED FURTHER READING*

S Haskins, et al.: Reference cardiopulmonary values in normal dogs. *Comp Med*. **55**, 2005, 156, *An excellent reference article reporting data collected from 97 healthy, unsedated, normovolemic dogs. Mean cardiac index for these dogs reported to be 4.44 L/min/m*^{2}.

MS Mellema: Cardiac output, wedge pressure, and oxygen delivery. *Vet Clin North Am Small Anim Pract*. **31**(6), 2001, 1175, *A more detailed presentation of the topic by this author. Although lacking a discussion of newer minimally invasive methods of cardiac output measurement, contains a more detailed discussion of relevant cardiovascular physiology for the interested reader*.

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* See the CD-ROM for a complete list of references

152 Chapter 152 Traumatic Brain Injury

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152.1 KEY POINTS

- Identification and management of extracranial disorders, such as systemic hypotension, hypoxemia, and hypoventilation, should be the first priority when treating a patient with acute traumatic brain injury (TBI).
- Mannitol is effective in treating intracranial hypertension, but it can compromise cerebral perfusion if its osmotic diuretic effects are not ameliorated rapidly with intravascular volume replacement.
- Hypertonic saline (7% to 8%) is effective in treating intracranial hypertension and is less likely to lead to hypovolemia and decreased cerebral perfusion.
- Corticosteriods are not recommended for the treatment of TBI.
- Prognosis varies, but even patients with severe neurologic deficits can recover with aggressive supportive care.

152.2 INTRODUCTION

152.2.1 Incidence and Prevalence of Head Injury

Traumatic injuries (TBIs) are common in dogs and cats, with motor vehicle accidents, animal interactions, and unknown etiologies being the most common causes seen in a multicenter study of 1099 dogs and 191 cats.[1] In that study, 26% of dogs and 42% of cats had evidence of head injury. Other common causes of head injury in dogs and cats include falls from heights, blunt trauma, gunshot wounds, and other malicious human activity.[2] The overall prevalence and incidence of head injury in veterinary medicine has not been well studied, but a retrospective study from a large, urban veterinary hospital reported an average of 145 cases of confirmed TBI per year from 1997 to 1999.[3]

152.2.2 General Approach to the Patient With a Head Injury

When treating a patient with an acute head injury, both extracranial and intracranial priorities must be acknowledged and evaluated. Identification of life-threatening extracranial injuries such as hemorrhage, penetrating thoracic or abdominal wounds, airway obstruction, and compromise of oxygenation, ventilation, or volume status is of paramount importance. Once life-threatening extracranial factors have been identified, intracranial priorities should include maintenance of adequate cerebral perfusion pressure (CPP), ensuring adequate oxygen delivery to the brain, and treatment of acute intracranial hypertension, as well as continued monitoring of neurologic status.

152.3 PATHOPHYSIOLOGY

The underlying injuries that result from head trauma can be separated into two categories: primary injury and secondary injury. Primary injury occurs as an immediate result of the traumatic event. Secondary injury occurs during the hours to days after trauma and is caused by a complex series of biochemical events, including release of inflammatory mediators and excitatory neurotransmitters, and changes in cellular membrane permeability.

152.3.1 Box 152-1 Most Common Factors Leading to Secondary Brain Injury

- Excitotoxicity
- Ischemia
- Inflammation
- ATP depletion
- Production of reactive oxygen species
- Accumulation of intracellular sodium and calcium
- Nitric oxide accumulation
- Cerebral lactic acidosis

ATP, Adenosine triphosphate.

152.3.2 Primary Injury

The least severe primary brain injury is concussion, characterized by a brief loss of consciousness. Concussion is not associated with any underlying histopathologic lesion.[4] Brain contusion consists of parenchymal hemorrhage and edema. Clinical signs can range from mild to severe. Contusions can occur in the brain directly under the site of impact ("coup" lesions), or in the opposite hemisphere ("contrecoup" lesions), or both, as a result of displacement of the brain within the skull. Although mild contusion can be difficult to differentiate from concussion, unconsciousness for more than several minutes is most consistent with contusion.[2]

Laceration is the most severe of primary brain injury and is characterized by physical disruption of the brain parenchyma. Axial hematomas within the brain parenchyma and extraaxial hematomas in the subarachnoid, subdural, and epidural spaces can occur, causing compression of the brain and leading to severe localizing signs or diffuse neurologic dysfunction.[5] The literature suggests that extraaxial hemorrhage is rare in dogs and cats after head injury; however, there is mounting evidence that this type of hemorrhage occurs in up to 10% of animals with mild head injury and more than 80% of dogs and cats with severe head injury.[5,6]

152.3.3 Secondary Injury

TBI triggers a series of biochemical events that ultimately result in neuronal cell death. Box 152-1 is a list of the most common types of secondary injury. These secondary injuries are caused by a combination of intracranial and systemic insults that occurs in both independent and interrelated ways.

Systemic insults that contribute to secondary brain injury include hypotension, hypoxia, systemic inflammation, hyperglycemia, hypoglycemia, hypercapnia, hypocapnia, hyperthermia, electrolyte imbalances, and acid-base disturbances. Intracranial insults include increased intracranial pressure (ICP), compromise of the blood-brain barrier, mass lesions, cerebral edema, infection, vasospasm, and seizures. All of these factors ultimately lead to neuronal cell death.[7]

Immediately after injury, there is massive release of excitatory neurotransmitters that causes influx of sodium and calcium into neurons, resulting in depolarization and further release of excitatory neurotransmitters. Increased influx of calcium overwhelms mechanisms for removal, causing severe intracellular damage and ultimately neuronal cell death.[8] Excessive metabolic activity also results in depletion of adenosine triphosphate (ATP) stores.

Several factors favor the production of reactive oxygen species after TBI, including hypoperfusion and local tissue acidosis. Hemorrhage provides a source of iron, which favors the production of hydroxyl radicals. Catecholamines may also contribute to the production of free radicals by direct and indirect mechanisms. These reactive oxygen species then oxidize lipids, proteins, and deoxyribonucleic acid (DNA), resulting in further destruction of neurons. Because the brain provides a lipid-rich environment, it is particularly susceptible to oxidative injury.

Nitric oxide has been associated with perpetuation of secondary brain injury after trauma, most likely due to its vasodilatory effects and its participation in free radical reactions, but the exact mechanism is not well understood.[8]

TBI is associated with production of inflammatory mediators.[9] These mediators perpetuate secondary brain injury via a number of mechanisms, including inducing nitric oxide production, triggering influx of inflammatory cells, activating the arachidonic acid and coagulation cascade, and disrupting the blood-brain barrier. Because studies have shown both neuroprotective and neurotoxic effects of inflammation, research is focusing on the development of targeted antiinflammatory agents that preferentially affect the more acute, destructive inflammatory processes.[9]

Primary and secondary intracranial injuries, in combination with systemic effects of the trauma, ultimately result in worsening of cerebral injury as a result of a compromised CPP, the force driving blood into the calvarium and providing the brain with essential oxygen and nutrients. CPP is defined as the difference between mean arterial blood pressure (MAP) and ICP.

Blood flow to the brain per unit time, or cerebral blood flow (CBF), is a function of CPP and cerebrovascular resistance. The normal brain is capable of maintaining a constant CBF over a wide range of MAP (50 to 150 mm Hg) via autoregulatory mechanisms. However, the traumatized brain often loses much of this autoregulatory capacity, making it susceptible to ischemic injury with even small decreases in MAP.

The following equation summarizes the “Monro-Kellie Doctrine,” developed in the early nineteenth century to describe intracranial dynamics:

$$V_{\text{intracranial}} = V_{\text{brain}} + V_{\text{CSF}} + V_{\text{blood}} + V_{\text{mass lesion}}$$

where V = volume. Sudden increases in any of these volumes as a result of primary and secondary brain injuries can lead to dramatic increases in ICP.

Initially, increases in ICP will trigger the Cushing reflex, or central nervous system ischemic response, a characteristic rise in MAP and reflex decrease in heart rate (see Chapter 100, Intracranial Hypertension). The central nervous system (CNS) ischemic response in a patient with head trauma is a sign of a potentially life-threatening increase in ICP and should be treated promptly.

Table 152-1 Interpretation of Pupil Size and Pupillary Light Response in Head Trauma

Pupil Size	Response to Light	Level of Lesion	Prognosis
Midposition	Normal	—	Good
Bilateral miosis	Poor to none	Cannot localize	Variable
Unilateral mydriasis	Poor to none	Cranial nerve III	Guarded to poor
Unilateral mydriasis and ventrolateral strabismus	Poor to none	Midbrain	Guarded to poor
Midposition	None	Pons, medulla	Poor to grave
Bilateral mydriasis	Poor to none	—	Poor to grave

152.4 NEUROLOGIC ASSESSMENT

Initial neurologic examination should focus on the level of consciousness, posture, and pupil size and response to light (Table 152-1). A more detailed neurologic examination can be performed once stabilizing therapy has been instituted. Based on findings from this examination, a score can be assigned to grade the severity of injury (see Chapter 97, Coma Scales). The initial neurologic examination should be interpreted in light of the cardiovascular and respiratory system because shock can have a significant effect on neurologic status, reducing the patient's level of consciousness and pupillary responses.

152.5 DIAGNOSTIC TESTS AND MONITORING

Because of the likelihood of multisystemic injury associated with head trauma, initial diagnostic tests and patient monitoring should focus upon a global assessment of patient stability. Emergency blood screening should consist of a packed cell volume and total solids determination to assess for hemorrhage, blood glucose to assess the severity of injury,[3] and a blood gas (venous or arterial) to assess ventilation, perfusion, and acid-base status. When available, electrolyte, lactate, and renal values, and markers of hepatic damage should also be obtained before therapy is instituted. Serial monitoring of these values is essential because dramatic changes can occur with therapy. Jugular venipuncture should be avoided because occlusion of the jugular vein can result in marked increases in ICP as a result of decreased venous outflow from the brain.

Diligent monitoring of the cardiovascular and respiratory systems is imperative to minimize the risk of secondary brain injury. For each episode of hypoxemia or hypotension, the prognosis for neurologic recovery dramatically decreases in human patients with TBI.[10] Basic monitoring of the cardiovascular system focuses on maintenance of adequate tissue perfusion (pink mucous membranes, capillary refill time of 1 to 2 seconds, good peripheral pulse quality, and a normal heart rate). In addition, systemic blood pressure should be monitored routinely. MAP should be maintained at or above 80 mm Hg in order to maintain CPP. Blood pressure as measured with the Doppler technique should be maintained above 100 mm Hg because this value is thought to represent the systolic blood pressure in small animals. Heart rate should be assessed when hypertension (MAP >100 mm Hg or systolic >120 mm Hg) is present. If evidence of the central nervous system ischemic response is present, therapy directed toward lowering ICP should be instituted. Alternatively, hypertension associated with tachycardia suggests pain or anxiety, which should be treated.

Monitoring of the respiratory system focuses on maintenance of oxygenation and ventilation. Oxygenation can be assessed via pulse oximetry, with a goal of maintaining saturation above 94%. When arterial sampling is possible, oxygen tension should be maintained above 80 mm Hg. If oxygenation cannot be monitored, oxygen should be supplemented. Failure to maintain oxygenation above these levels may warrant intubation and positive-pressure ventilation.

Ventilation can be assessed by blood gas analysis or end-tidal capnometry. Although arterial blood gas sampling is the gold standard for assessing carbon dioxide tension, a venous blood gas can be substituted if tissue perfusion is normal. Venous carbon dioxide concentrations will exceed arterial by 2 to 5 mm Hg; however, this difference is exacerbated with poor tissue perfusion. End-tidal capnometry tends to underestimate arterial carbon dioxide tension by 5 mm Hg, and changes in cardiac output can significantly alter the values obtained.

Radiographs of the skull in patients that have sustained head trauma are an insensitive diagnostic tool and rarely provide valuable information. Computed tomography (CT) is the preferred imaging method. CT scans are superior to magnetic resonance imaging (MRI) for assessing bone and areas of acute hemorrhage or edema. As the time from injury increases, or when subtle neurologic deficits are present, MRI becomes a more useful tool.[11] Advanced imaging provides information about mass lesions (epidural, subdural, or intraparenchymal hemorrhage) or depressed skull fractures that may require surgical intervention. Such studies should be considered in patients with moderate to severe signs on presentation, lateralizing signs, or failure to improve significantly within the first few days or those with an acute deterioration in neurologic status.

152.6 TREATMENT

When formulating a treatment plan for a patient with TBI, both intracranial and extracranial concerns must be addressed. Extracranial priorities include ventilation, oxygenation, and maintenance of normal blood pressure, and intracranial priorities include treatment of intracranial hypertension and control of cerebral metabolic rate.

152.6.1 Extracranial Therapy

The first priority in treating a patient with head trauma is extracranial stabilization. As with any severely injured patient, the basics of airway, breathing, and circulation should be evaluated and addressed if necessary. Patency of the airway should be assessed as soon as possible and treated with endotracheal intubation or emergency tracheostomy, if indicated. The pharynx and larynx should be inspected visually and suctioned as needed to maintain airway patency. Hypoxia is also common, and supplemental oxygen is indicated in the initial treatment of all patients with significant head injury. Increases in the blood CO_2 concentration can lead to cerebral vasodilation and increased intracranial blood volume, worsening ICP (see Secondary Injury section). Conversely, hypocapnia due to hyperventilation can lead to cerebral vasoconstriction, decreasing cerebral blood flow and leading to cerebral ischemia. Therefore CO_2 should be maintained at the low end of the normal range in patients with head trauma (e.g., venous CO_2 40 to 45 mm Hg, arterial CO_2 35 to 40 mm Hg).[12] In some patients, this will require mechanical ventilation (see Chapter 213, Basic Mechanical Ventilation).

Patients with head trauma commonly present in hypovolemic shock, and volume resuscitation goals should be aggressive (MAP of 80 to 100 mm Hg, see Chapter 65, Shock Fluids and Fluid Challenge). For patients without electrolyte disturbances, normal saline (0.9%) is the best inital choice for fluid resuscitation because it contains the smallest amount of free water (sodium concentration 154 mEq/L) of the isotonic fluids and is therefore least likely to contribute to cerebral edema. Colloid resuscitation may also prove beneficial. For hydrated patients with evidence of hypovolemia and increased ICP, a combination colloid and hyperosmotic (hypertonic saline) solution is recommended (see Intracranial Therapy later in this chapter and Table 152-2). Patients that do not respond to volume resuscitation require vasopressor support (see Chapter 176, Vasoactive Catecholamines).

152.6.2 Intracranial Therapy

152.6.2.1 Hyperosmotic Agents

Mannitol has been shown to decrease ICP, increase CPP and CBF, and have a beneficial effect on neurologic outcome in patients with head injury.[13] Mannitol may also possess free radical scavenging properties. Its positive effects can be seen clinically within minutes of administration, most likely a result of its rheologic its effects (decreased blood viscosity) causing an increase in CBF and cerebral oxygen delivery. Within 15 to 30 minutes, its osmotic effects predominate, drawing water out of the brain parenchyma (primarily normal tissue) and into the intravascular space. These effects can last from 1.5 to 6 hours. In humans, mannitol may induce acute renal failure if serum osmolarity exceeds 320 mOsm/L, suggesting that serial measurement of serum osmolality may be useful in patients receiving repeated doses.[14] Mannitol may cause increased permeability of the blood-brain barrier, allowing it to leak into the brain parenchyma where it can exacerbate edema. Because this effect is most pronounced when mannitol remains in the circulation for long periods, the drug should be administered as repeated boluses rather than as a constant rate infusion.[13] Mannitol boluses of 0.5 to 1.5 g/kg have been recommended for the treatment of ICP in dogs and cats.[15] High-dose mannitol therapy (1.4 g/kg) resulted in significiant neurologic improvement compared to low-dose therapy (0.7 g/kg) in 44 people with head injury.[16] Treatment must be followed with isotonic crystalloid solutions or colloids, or both, to maintain intravascular volume.

Hypertonic saline is an alternative hyperosmotic solution that may have advantages over mannitol in some 660 patients with head injury. Because sodium does not freely cross the blood-brain barrier, hypertonic saline has 661 similar rheologic and osmotic effects to mannitol. In addition, it improves hemodynamic status and has beneficial vasoregulatory and immunomodulatory effects.[17] Because sodium is reabsorbed in the kidneys, hypotension is a less likely sequela than with mannitol, making it a better choice for patients with increased ICP and systemic hypotension. Hypertonic saline can be administered with a colloid in such cases to allow for a more prolonged volume expansion effect (see Table 152-2).

Table 152-2 Drugs, Fluids, and Dosages for the Treatment of Patients With Head Trauma

Indication	Drug or Fluid	Dosage	Notes
Any patient with evidence of head trauma and hypotension	Isotonic crystalloid solution (0.9% saline preferred)	Administer boluses of one fourth to one third of the shock dose (shock dose = 90 ml/kg for the dog, 60 ml/kg for the cat)	May repeat as needed Consider colloid boluses if no response after 2 to 3 crystalloid boluses
Increased ICP in normotensive or hypertensive patients	Mannitol 25%	0.5 to1.5 g/kg IV over 15 minutes	Use filter during administration; can lead to severe dehydration; follow with isotonic crystalloids to prevent dehydration and hypovolemia
		May repeat	Closely monitor intake and output
Increased ICP in hypovolemic or hypotensive patients	HTS (7%)* plus dextran-70 or hydroxyethyl starch	3 to 5 ml/kg IV over 15 minutes	Do not use in hyponatremic patients
		May repeat	Monitor serum sodium levels
Increased ICP, normotensive, hypertensive, or hypotensive patients	HTS (7% to 7.8%)†	3 to 5 ml/kg IV over 15 minutes	Do not use in hyponatremic patients
		May repeat	Monitor serum sodium levels

HTS, Hypertonic saline; *ICP,* intracranial pressure; *IV,* intravenous.

* If using 23.4% HTS, dilute 1 part HTS with 2 parts sterile water or normal saline.

† If using 23.4% HTS, dilute 1 part HTS with 2 parts dextran-70 or hydroxyethyl starch. If using 7% to 7.5% HTS, administer separate doses of HTS and colloid (3 to 5 ml/kg HTS, 2 to 3 ml/kg artificial colloid).

152.6.2.2
Corticosteroid

Corticosteroids are potent antiinflammatory agents and have historically been used extensively in human and veterinary medicine to treat patients that have sustained head trauma. A clinical trial evaluating over 10,000 human adults with head injury showed that corticosteroid treatment was associated with worse outcomes at 2 weeks and 6 months after injury.[18,19] The Brain Trauma Foundation recommends that corticosteriods not be administered to patients with TBI.[13]

152.6.2.3
Furosemide

Furosemide has been used in patients with head trauma either as a sole agent to reduce cerebral edema or in combination with mannitol to decrease the initial increase in intravascular volume and hydrostatic pressure associated with the drug. However, the use of this drug as a sole agent in patients with head trauma has been called into question because of the potential for intravascular volume depletion and systemic hypotension, leading to decreased CPP.[20] The Brain Trauma Foundation guidelines do not recommend that furosemide be used in combination with mannitol.[13] Therefore it should be reserved for those patients in whom it is indicated for reasons other than cerebral edema, such as those with pulmonary edema or oliguanuric renal failure.

152.6.2.4

Decreasing Cerebral Blood Volume

Techniques to decrease CBV have been proposed as methods for lowering increased ICP. Elevation of the head by 15 to 30 degrees reduces CBV by increasing venous drainage, decreasing ICP, and increasing CPP without deleterious changes in cerebral oxygenation.[21] A slant board should be used instead of pillows or towels to prevent occlusion of the jugular veins by bending of the neck. Higher elevations of the head may cause a detrimental decrease in CPP.

Prevention of hypoventilation, as described above, can reduce cerebral vasodilation and decrease CBV. The goal should be normocapnia (arterial carbon dioxide of 35 to 40 mm Hg). In cases of acute intracranial hypertension, short-term hyperventilation to an arterial carbon dioxide of 25 to 35 mm Hg may be used to reduce CBV and ICP, but long-term hyperventilation is not recommended because of evidence that the decrease in CBF leads to cerebral ischemia and worsens outcome.[13]

152.6.2.5

Decreasing Cerebral Metabolic Rate

Increased cerebral metabolic rate after head injury due to excitotoxicity and inflammation can lead to cerebral ischemia and cellular swelling, increasing ICP. Interventions that decrease cerebral metabolic rate may lessen secondary brain injury. Although rarely used in veterinary medicine, induction of a barbiturate coma and therapeutic hypothermia have been used in experimental studies and clinical trials in humans and can be effective in decreasing ICP and improving outcome in patients with refractory intracranial hypertension.[22] The Brain Trauma Foundation states that there is insufficient evidence to publish treatment standards on the use of barbiturates, but this therapy may be considered in patients with elevated ICP that is refractory to medical and surgical therapy.[13]

152.7

PROGNOSIS

The prognosis is difficult to predict following TBI. Although the initial neurologic status may be helpful in predicting outcome, reassessment after stabilizing therapy is recommended because the level of consciousness may improve once tissue perfusion has been corrected. Pupillary dilation, loss of pupillary light responses, and deterioration in the level of consciousness during therapy are poor prognostic indicators (see Table 152-1). It is likely that younger animals, particularly kittens, can make remarkable recoveries despite severe dysfunction immediately following trauma, although definitive research is lacking. Owners should be aware that animals who survive severe TBI may be left with persistent neurologic deficits, which may take months to resolve or may never resolve. These animals can also develop delayed seizure disorders. 661 662

The Small Animal Coma Scale was developed to quantitatively assess functional impact of brain injury (see Chapter 97, Coma Scales). This scale assesses three major categories: motor activity, level of consciousness, and brain stem reflexes. Although this scale has not been validated prospectively in animals, it has been shown retrospectively to correlate with 48-hour outcome in dogs with head trauma.[23] This may be most useful when evaluated serially in patients to determine if there has been improvement or deterioration following treatment.

In human medicine, hyperglycemia at admission and persistence of hyperglycemia have been associated with worsened mortality and outcome.[24] Hyperglycemia has been associated with more severe injury in head-injured veterinary patients[3] but has not been validated as an independent predictor of outcome.

152.8 SUGGESTED FURTHER READING*

C Dewey, S Budsberg, J Oliver, et al.: Principles of head trauma management in dogs and cats. Part II. *Comp Cont Educ Pract Vet*. **15**, 1993, 177, *A useful overview of treatment strategies for dogs and cats with head trauma*.

SR Platt, ST Radaelli, JJ McDonnell, et al.: The prognostic value of the modified Glasgow Coma Scale in head trauma in dogs. *J Vet Intern Med*. **15**, 2001, 581, *A retrospective study showing that modified Glasgow Coma Scale score predicted 48-hour survival in dogs with TBI.*

BJ Zink: Traumatic brain injury. *Emerg Med Clin North Am*. **14**, 1996, 115, *A thorough description of the pathophysiology of TBI, with emphasis on biochemical pathways. Also provides management guidelines*.

* See the CD-ROM for a complete list of references

153 Chapter 153 Thoracic Trauma

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153.1 KEY POINTS

- Thoracic injuries are common in any animal suffering from significant trauma.
- Multiple thoracic injuries often coexist in an individual patient.
- The diagnosis of thoracic trauma is typically made from the history, physical examination, and imaging techniques (e.g., thoracic radiographs).
- Pulmonary contusions are the most common thoracic injury. Other injuries include pneumothorax, diaphragmatic hernia, and rib fractures.
- Because of the structure and resilience of the chest wall, animals are able to sustain high forces to the thorax without demonstrating signs related to thoracic trauma.
- Life-threatening injuries are uncommon; however, aggressive medical and surgical management may be necessary.
- Mechanical ventilation may be warranted in cases of severe respiratory compromise, pain, or respiratory failure.

153.2 INTRODUCTION

Injury to the respiratory system is common in any animal suffering from significant trauma. It has been estimated that 39% of dogs that incur skeletal injuries due to motor vehicular accidents also sustain thoracic injury. Of those injuries, pulmonary contusions predominate.[1,2] Over one half of the animals suffering from thoracic trauma have more than one thoracic injury.[1] Therefore it is imperative that the myriad of potential thoracic injuries be identified rapidly and treated appropriately. Thoracic injuries may vary in severity from those less likely to result in significant morbidity and mortality to those that are life threatening and warrant immediate intervention. This chapter will focus on the more common thoracic injuries, including the pathophysiology and treatment of these injuries.

153.3 PNEUMOTHORAX

The pleural space is a potential space that is created by the opposing surfaces of the parietal pleura and the visceral pleura (see Chapter 30, Pleural Space Disease). The normal pleural space is occupied by only a small amount of serous fluid that helps lubricate the surfaces of the pleurae. This space also maintains a resting negative intrathoracic pressure relative to the atmosphere. When this negative intrapleural pressure is not maintained, there is disruption of the normal expansive and relaxation properties of the lung. A pneumothorax is created when air accumulates within the pleural space. Air can be introduced into the pleural space via two mechanisms: alveolar rupture secondary to increased force applied to the chest with a closed glottis or secondary to laceration of the pulmonary parenchyma.[3] Progression of the pneumothorax will depend on several factors: the respiratory pattern of the patient, the size of the defect, and whether the defect is unidirectional, prohibiting the escape of air from the pleural space.[4]

Air in the pleural space can lead to partial or complete lung atelectasis and disturbances in pulmonary and cardiac hemodynamics.[3] Ventilation-to-perfusion mismatch is a result of instantaneous lung collapse and results in a decreased arterial partial pressure of oxygen. Minute ventilation is maintained by an increased respiratory rate that compensates for decreased tidal volume.[4] However, if there is severe atelectasis from increased air in the pleural space, hypoxemia develops rapidly and overwhelms compensatory mechanisms. For example, a tension pneumothorax develops when the intrathoracic pressure exceeds the atmospheric pressure. This causes a decrease in venous return and can cause complete respiratory and hemodynamic collapse.[3] If pleural pressure exceeds central venous and pulmonary artery pressures, there is decreased venous return to the heart. Tachycardia results in an effort to maintain cardiac output. Systemic hypotension results when the myocardial oxygen demand is higher than delivery, thus further decreasing cardiac output.[4] These patients often present with clinical signs of shock, similar to that witnessed with cardiac tamponade, because atrial diastolic filling is compromised by decreased venous return to the heart from the increased intrapleural pressure.[3]

A pneumothorax may be open or closed. An open pneumothorax occurs when the pleural space communicates directly with the atmosphere. In this situation, the unaffected lung is not ventilated normally and there is a paradoxical decrease in pulmonary volume with inspiration and an increase on exhalation.[3] A *sucking chest wound* is present if air is heard moving in and out of the pleural space with respirations.[3] With a closed pneumothorax, air is contained within the pleural space. This may be accompanied by other signs of thoracic trauma (e.g., rib fractures) and may be a result of damage to the larger nonconducting airways (trachea and bronchi), other mediastinal structures (esophagus), or the pulmonary parenchyma itself (most common).[3,4]

Diagnosis is made most commonly with thoracic radiographs, although a high clinical suspicion should exist based on physical examination alone. Dull dorsal breath sounds and hyperresonance on percussion of the affected lung dorsally are hallmarks of a pneumothorax. The best radiographic view is a ventrodorsal view. Radiography often reveals that a can cause retraction of the lungs from the body wall, elevation of the heart off the sternum, and atelectasis in patients with a pneumothorax.[5] A diagnosis of tension pneumothorax is often suspected in patients that are air hungry, tachycardic, tachypneic, and cyanotic.[3] In this case, immediate therapy is vital, and waiting for a thoracic radiograph may prove fatal.

The goal of treatment for pneumothorax is reexpansion of the collapsed lung. This may be accomplished by thoracocentesis or tube thoracostomy if the volume of air is such that negative pressure cannot be established within the pleural space or if repeated thoracocenteses are required (see Chapters 31 and 32, Thoracentesis and Thoracostomy Tube Placement and Drainage, respectively). Intermittent or continuous pleural drainage will be necessary following thoracostomy tube placement, depending on the rate of air accumulation. If an animal with a rapidly progressive pneumothorax presents, an immediate thoracotomy and intubation with positive-pressure ventilation may prove lifesaving. If an open pneumothorax is present, an occlusive dressing should be placed to create a closed pneumothorax. The dressing should be secured only on three sides to allow for air escape from the pleural space without risk of developing a tension pneumothorax.[3] Alternatively, a full occlusive dressing can be placed and secured on all four sides if a thoracostomy tube is inserted.

Open chest wounds will require surgical exploration once the patient has been stabilized. Treatment decisions should be based on the respiratory and cardiovascular status of the patient. In an otherwise stable patient, repeated monitoring (physical parameters, pulse oximetry, and arterial blood gases) can take the place of immediate evacuation of the pleural space.

According to one study, the prognosis for patients with pneumothorax may depend on the need for thoracocentesis and the length of the intensive care unit stay. Animals that required repeated thoracocenteses or had shorter hospitalizations were more likely to be euthanized in one study. Animals that present dyspneic also tended to have a poorer prognosis.[6] Overall, the prognosis for animals with a traumatic pneumothorax is good, with an 87% survival rate reported.[6] However, animals may succumb to other serious concurrent injuries.

153.4 PULMONARY CONTUSIONS

Pulmonary contusions are the most common type of injury following blunt thoracic trauma (see Chapter 25, Pulmonary Contusions and Hemorrhage).[7] The most frequent cause in human medicine is motor vehicle accidents; other possible causes include falls and penetrating chest trauma.[3] In veterinary medicine, 17% of animals have evidence of pulmonary contusions after a motor vehicle accident.[8] Pulmonary contusions rarely exist as an isolated injury and are often found in association with other thoracic injuries (e.g., rib fractures, pneumothorax, hemothorax, diaphragmatic hernia) (see Chapter 25, Pulmonary Contusions and Hemorrhage).[7]

153.5 RIB FRACTURES

Rib fractures may occur secondary to any thoracic trauma and are the most common type of thoracic injury in human patients. Rib fractures rarely occur in isolation and often occur in conjunction with pulmonary contusions or pleural space disease.[3] They may be evident on initial physical examination if a flail segment or open fracture is present. However, a majority of rib fractures are most readily diagnosed with thoracic radiographs. It seems that the ribs can sustain forces greater than other long bones before a fracture occurs. Human cadaver studies indicate that the thorax can tolerate a 20% volume reduction before rib fractures occur.[3] However, underlying lung tissue can sustain significant injury as a result of the concussive forces of the traumatic event.[5]

Rib fractures may cause hypoxemia indirectly by leading to lung injury; therefore oxygen supplementation is warranted. Rib fractures may also lead to hypoventilation as a result of pain. Pain management is of utmost importance and may consist of local or systemic use of analgesics. Local anesthetic agents (i.e., lidocaine and/or bupivacaine) are useful because they do not inhibit ventilation. Local blocks should be administered to the caudal surface of the fractured rib(s), both dorsally and ventrally to enhance efficacy.[5] Systemic analgesia should be used cautiously to prevent respiratory depression.

153.6 FLAIL CHEST

Flail chest is a relatively uncommon condition in veterinary patients, but occurs most commonly secondary to dog-bite trauma and motor vehicle trauma.[9] Flail chest occurs secondary to the fracture of two or more adjacent rib segments, both dorsally and ventrally. This segmental chest wall injury can lead to thoracic instability and paradoxical chest wall motion.[3,10] Intrathoracic injuries affect respiratory function more than the rib fractures themselves.

Pulmonary contusions have the greatest effect on oxygenation and ventilation, but hemothorax or pneumothorax and pain will also affect pulmonary mechanics.[3] Patients usually present tachypneic or dyspneic, with paradoxical motion of the chest wall flail segment (see following paragraph). In most patients, the diagnosis is confirmed with thoracic radiography. Radiographs often reveal the flail segment and also highlight any concurrent injuries (pulmonary contusions or pleural space disease).

The flail component moves paradoxically in relation to the rest of the thorax. The flail segment moves inward with inspiration as a result of the negative intrathoracic pressure and outward with exhalation. The flail segment has been shown to cause a small reduction in the arterial partial pressure of oxygen, although this does not appear to be significant in experimental studies.[10] In humans, the incidence of concomitant injuries, such as pulmonary contusions and a pneumothorax, are 50% and 77%, respectively.[3] In animals, the likelihood of pulmonary contusions secondary to flail chest is estimated to be between 75% to 100%.[11] These injuries, in combination with pain, contribute the most to the hypoxemia and hypoventilation that occur in patients with flail segments.

Treatment of the underlying intrathoracic injuries depends on the severity of the injuries. Hypoxemia secondary to pulmonary contusions may require oxygen supplementation, and mechanical ventilation may be necessary for patients in respiratory failure (see Chapters 19 and 213, Oxygen Therapy and Basic Mechanical Ventilation, respectively). Pneumothorax may warrant thoracocentesis, placement of a chest tube, or an emergency thoracotomy. Hemothorax is usually self-limiting and related to the initial trauma,[10] but may require surgical exploration if continued hemorrhage is suspected. Although rare, cases of cardiac rupture or aortic or great vessel laceration have been reported.[10] Stabilization of the flail segment is often not necessary, but it should be considered if there is evidence of an open pneumothorax, continued hemothorax, or other evidence of continued trauma to the underlying tissues,[5] and/or an exploratory thoracotomy is otherwise warranted. Additionally, patients that require mechanical ventilation as a result of severe intrathoracic injuries and respiratory failure may benefit from stabilization of the flail segment.[10]

Treatment is most dependent on assessment of pulmonary function. Pain management should be considered early, because pain impairs normal chest wall movement and ventilation (see Chapters 161 and 164, Pain and Sedation Assessment and Analgesia and Constant Rate Infusions, respectively). Pain contributes not only to hypoventilation, but also to atelectasis and a decreased cough reflex, allowing the accumulation of pulmonary secretions.[9] The latter increases the likelihood for pneumonia. As with single rib fractures, local anesthetics provide analgesia without affecting ventilation centrally. The fractured ribs should be injected both dorsal and ventral to the fracture on the caudal surface of the rib. One rib caudal and cranial to the segment should also be included in the nerve block. Bupivacaine or lidocaine, or both, can be administered every 6 hours as needed. Epidural analgesia has shown improved benefit over patient-controlled analgesia in human medicine[3] and may be underutilized in veterinary patients. Because of the potential for hypotension, cardiovascular stability is a prerequisite to epidural analgesia. Systemic analgesia with opioids is also effective, but they should be employed cautiously to minimize respiratory depression. Placing the animal in lateral recumbency with the flail segment down or a light external chest wrap may prevent excessive outward movement of the segment.

153.7 HEMOTHORAX

Hemothorax occurs when blood collects in the pleural space. Hemothorax may result from injury to the lung parenchyma, chest wall and associated vessels, or great vessels. Generally, animals with severe injuries to the great vessels causing massive hemothorax do not survive long enough for a diagnosis to be made.[5] The clinical picture may be similar to that of patients with a pneumothorax and includes rapid, shallow respirations. However, the pleural space can accommodate large volumes of blood (50 to 60 ml/kg) without causing outward signs of respiratory compromise.[11] These patients may have dull heart and lung sounds ventrally and may be in shock secondary to hemorrhage.

The diagnosis of hemothorax is made by thoracocentesis. Nonclotting blood within the pleural space confirms the diagnosis. Radiographs and thoracic ultrasound may be helpful in determining relative quantities of pleural effusion and for monitoring purposes. However, clinical signs should determine treatment. Blood does not have to be removed from the pleural space unless it is causing respiratory compromise. Medical treatment for hypovolemic shock should consist of a combination of crystalloids, colloids, and/or blood products as indicated, including autotransfusion if necessary (see Chapters 65 and 66, Shock Fluids and Fluid Challenge and Transfusion Medicine, respectively). Significant hemorrhage may dictate volume replacement with packed red blood cells or whole blood, and ongoing hemorrhage indicates the need for exploratory thoracotomy.

153.8 PENETRATING CHEST WOUNDS

Chest wounds occur most commonly secondary to bite wounds, accounting for approximately 30% of all chest injuries in small animals.[12] Bite wounds to the upper airway, trachea, or chest wall can cause severe respiratory distress. Patients with upper airway compromise may require endotracheal intubation with positive-pressure ventilation if the trauma precludes adequate respiratory function. If the larynx cannot be visualized or the degree of upper airway trauma is such that endotracheal intubation is not possible, a tracheostomy may be necessary (see Chapter 18, Tracheostomy).

Penetrating thoracic bite wounds may cause a pneumothorax or hemothorax or may damage the lung parenchyma, resulting in pulmonary contusions. Thoracic radiographs are helpful in determining if a bite wound has penetrated the thorax but should be reserved for stable patients. Dyspneic patients will require supplemental oxygen and/or evacuation of the pleural space via thoracocentesis, placement of a thoracostomy tube, or thoracotomy, if necessary. Wounds may be sealed temporarily with a water-soluble gel and then covered with a sterile bandage until surgical exploration and repair is possible.[13]

Because of the high likelihood for bacterial contamination of these wounds, all animals should be placed on broad-spectrum antibiotics and a culture and sensitivity performed. According to a recent study, the most likely contaminants are *Staphylococcus* spp, *Escherichia coli,* and other coliform bacteria.[12] The prognosis for bite wounds depends on the associated injuries. It has been estimated that 6% to 25% of patients with thoracic bite wounds die or are euthanized.[5,14]

153.9 GUNSHOT WOUNDS

In veterinary medicine, the most common projectile injury is related to gunshot wounds.[15] In a retrospective study, 26% of the wounds associated with gunshots involved the thorax.[16] Injuries occur secondary to laceration or crushing of tissues and can result in extensive trauma to adjacent tissues, as well as those in the direct path of the bullet. However, the lung tends to be somewhat resilient because of its elasticity, limiting the amount of tissue destruction.[15] Penetration of the thorax can cause damage to the great vessels and result in severe and massive hemorrhage. Animals may present with a hemothorax or pneumothorax.

These patients will be tachypneic or dyspneic and may require evacuation of the pleural space via thoracocentesis, tube thoracostomy, or thoracotomy (tension pneumothorax). Blood products may be the initial fluid of choice for volume resuscitation if significant blood loss has occurred (see Chapter 66, Transfusion Medicine). Bleeding tends to occur from the pulmonary arterial system, a low-pressure system, and often responds to management with tube thoracostomy.[16] Although surgical exploration of the thorax is not recommended routinely, it may be necessary in animals with continued hemorrhage or air leaks or if the esophagus or other vital structures are damaged.[15,16]

153.10 TRACHEOBRONCHIAL INJURY

Although uncommon, injury to the trachea or other nonconducting airways can be lethal. It has been shown in human studies that most patients suffering from tracheobronchial injury die before arriving at a hospital.[3] Also considered uncommon in veterinary medicine, most of the literature focuses on tracheal rupture in cats secondary to endotracheal intubation.[5] Traumatic injury may be the result of traction at the carina during thoracic compression, causing stretching and tearing of the trachea immediately cranial to the carina, increased intrabronchial pressure, especially against a closed glottis, and shearing forces on a fixed carina during deceleration.[3,5]

Tracheobronchial trauma is generally secondary to a fall or motor vehicle accident. Patients have varying degrees of respiratory distress and may even be asymptomatic initially. In cats, the mediastinum may allow continuity of the intrathoracic airway and limit immediate signs of dyspnea. These patients may present in respiratory distress several days post trauma as a result of a pneumothorax.[5,17] Clinical signs, when present, most often consist of tachypnea, dyspnea, and coughing.[5] If subcutaneous emphysema is present, tracheal trauma should be suspected. Thoracic radiographs may show a pneumomediastinum, pneumothorax, or evidence of tracheal discontinuity (bulging of the peritracheal or mediastinal tissues surrounding the site of rupture).[17] Bronchoscopy is still considered the gold standard for the diagnosis and is often necessary before surgical correction is possible.

153.11 HIGH-RISE SYNDROME

The injuries of high-rise syndrome are a result of deceleration trauma.[18] The extent of injury is thought to increase up to seven stories, a point just beyond terminal velocity in cats.[19] At the time terminal velocity is reached, the vestibular system is no longer stimulated and the cat's body takes on a more horizontal position. This enables it to distribute the impact over a wider surface area and helps to minimize injury.[19,20]

A triad of injuries to the head and face, extremities, and thorax is common to high-rise syndrome in dogs and cats.[18,19,21] Thoracic injury is the most commonly sustained injury related to high-rise syndrome in cats. According to Whitney and others,[19] thoracic trauma accounts for 90% of feline injuries. The most common thoracic injuries were pneumothorax (68%) and pulmonary contusions (63%). Although dogs can suffer from similar injuries, the extent and distribution of their injuries is different from cats and is dependent on the height of the fall and the landing surface. Dogs are also prone to more extremity and spinal cord injuries.[21]

Clinical signs of high-rise syndrome are often attributable to the degree of thoracic trauma. Most animals will present with some degree of tachypnea or dyspnea that may be related to thoracic trauma or pain and shock. Thoracic radiographs should be done for assessment purposes in all patients with high-rise injuries. In a recent study, thoracic trauma was noted in only 33.6% of cats; however, thoracic radiography was used only in those patients with abnormal respirations[22] and may have underestimated the degree of thoracic involvement. If pneumothorax is suspected, thoracocentesis or tube thoracostomy may be necessary. Assessment for other injuries, including those to the extremities, head and face, or spine, should be performed after the patients are treated for shock and respiratory compromise. Cats have a reported 90% survival rate[19] and in the study by Gordon and others,

[21] all but 1 of 81 dogs survived. However, other reports state that most dogs who suffer from injuries related to high-rise syndrome are euthanized.[20]

153.12 DIAPHRAGMATIC HERNIA

Trauma is the most common cause of diaphragmatic injury, accounting for 85% of the hernias noted in the largest study of dogs and cats.[23] Most of the injuries sustained concurrent with a diaphragmatic hernia were found caudal to the thorax. Bony lesions, including pelvic, pelvic limb, and rib fractures, were most common. Other injuries included hernias at other locations, myocardial contusions, hip luxations, and damage to the liver and urinary bladder.[23] The liver is the most likely organ to herniate through a ruptured diaphragm, followed by the small intestine, stomach, spleen, and omentum.[23] Most insults occur on the right side of the diaphragm, possibly because the gas-filled stomach sits on the left and cushions some of the force.[23,24] The pathogenesis may be related to a sudden rise in intraabdominal pressure. With an open glottis, this rise in intraabdominal pressure increases the pleuroperitoneal pressure gradient and causes a tear in the diaphragm.[23,24] The extent and location of the tear will determine which, if any, abdominal organs move into the thorax.

Clinical signs are often attributable to the herniated organs, pleural effusion associated with the herniated contents, and concurrent injuries. Hypoxemia may be the result of pleural effusion, decreased lung volume secondary to pulmonary compression by organs, and overinflation of adjacent alveoli. Hypoxemia may be exacerbated by concurrent thoracic injuries (pulmonary contusions, pneumothorax, or chest wall disease).[5,24] Patients may present with varying degrees of respiratory signs. Dull ventral heart sounds may be the result of pleural effusion or the presence of solid organs within the thoracic cavity. When the intrahepatic pressure increases more than 5 to 10 mm Hg, pleural effusion results from transudation of fluid from the hepatic capsule.[23,24] Intestinal borborygmi may be auscultated over the thorax if air is contained within the herniated intestines. Gastric dilation within the hernia can result in severe respiratory and cardiovascular collapse and gastric necrosis. The stomach may compress the caudal vena cava, leading to decreased venous return and subsequent decreased cardiac output.[5]

The diagnosis of diaphragmatic hernia is made most commonly with thoracic radiography. There appears to be a high correlation with radiographic signs and observations during surgery, indicating the value of thoracic radiography in the diagnosis of diaphragmatic hernia.[23] There may be loss of the normal diaphragmatic outline, air-filled intestines or stomach within the thoracic cavity, or displacement of the heart, lungs, or trachea by other soft tissue structures or effusion.[5,24] Because some hernias are not readily apparent with plain radiography, ultrasonography and positive contrast gastrography or peritoneography may be helpful in making a diagnosis.

Definitive treatment requires surgical repair of the hernia. There is some debate over the ideal timing of surgery. Some reports predict a poorer outcome in patients taken to surgery within 24 hours of injury,[25] although other studies do not support those findings.[26,27] Emergency surgery is necessary when the patient cannot be stabilized because lung expansion is severely compromised, or when there is strangulated viscera or evidence of gastric dilation within the thorax.[11]

All attempts should be made to stabilize the patient before surgical correction of the hernia. This should include fluid therapy to maximize cardiac output and oxygen delivery to the tissues, oxygen therapy to treat hypoxemia related to ventilation-to-perfusion abnormalities, and evacuation of the pleural space via thoracocentesis or tube thoracostomy for pleural effusion and pneumothorax. Care must be taken during thoracentesis or tube thoracostomy to prevent puncture or rupture of the herniated contents. Hemorrhage associated with splenic or hepatic damage may require blood transfusions.

Wilson and others[23] report a 30% mortality rate in dogs and cats within 24 hours to 7 days after the trauma, and Schmiedt and others[27] report an almost 18% mortality rate in cats during hospitalization. Some studies predict that the mortality is greatest for dogs and cats within 24 hours of surgery.[26] Concurrent thoracic trauma also decreases survival.[5] Death may be the result of hemothorax or pneumothorax, reexpansion pulmonary edema, cardiac arrhythmias, and multiple organ failure.[23,24,27]

153.13 MYOCARDIAL CONTUSIONS

Myocardial contusions are caused by a deceleration force acting on the chest wall. This force causes both direct compression of the myocardium and shearing stresses secondary to increased intrathoracic pressure.[28] Myocyte necrosis secondary to epicardial hemorrhage occurs with severe contusions.[28] The diagnosis of myocardial contusion is often based on abnormalities associated with an electrocardiogram (ECG) and evidence of hemodynamic compromise. In human medicine, echocardiography, cardiac enzymes, and radionuclear imaging often aid in the diagnosis.[28,29] A true diagnosis is one that depends on histopathology or gross examination of the heart.

Clinical signs are more typically related to the trauma, rather than any direct damage to the myocardium. Patients may be in respiratory distress from a concurrent pulmonary parenchymal or pleural space disease. Additionally, most patients have evidence of hypovolemic or hypoxemic shock. Most animals with significant thoracic trauma have alterations in their heart rate and rhythm, and repeated or continuous monitoring of the ECG is therefore recommended. Evidence of arrhythmias may not be present for 12 to 48 hours after injury, although most arrhythmias occur within 24 hours.[28,29] Sinus tachycardia is commonly present after trauma and may be the result of stress, pain, anemia, and/or hypovolemia.[29] This arrhythmia often responds to intravenous fluid therapy and correction of associated hypoxemia, anemia, electrolyte abnormalities, and ventricular arrhythmias, particularly VPCs, are the most common arrhythmia post trauma, but they rarely require treatment.[29] Evidence of ventricular arrhythmias usually abate within 72 hours of the trauma.

Treatment of the arrhythmia should be aimed at correction of associated shock and maintenance of euvolemia before considering antiarrhythmic therapy. Appropriate pain management is also necessary. If the ECG (rate and rhythm), blood pressure, and clinical status of the patient are compromised, antiarrhythmic therapy should be considered. Supraventricular arrhythmias may be treated with calcium channel blockers or β-blockers. Ventricular tachyarrhythmias can be treated with lidocaine or procainamide (see Chapter 190, Antiarrhythmic Agents).

153.14 SUGGESTED FURTHER READING*

DA Bjorling, GK Sicard: Diaphragmatic hernia. In LG King (Ed.): *Textbook of respiratory diseases in dogs and cats*. 2004, Saunders, St Louis, *Chapter that provides a great overview of diaphragmatic hernias, including anatomy of the diaphragm and the pathophysiology and management of hernias.*

DJ Brockman, DA Puerto: Pneumomediastinum and pneumothorax. In LG King (Ed.): *Textbook of respiratory diseases in dogs and cats*. 2004, Saunders, St Louis, *Chapter that provides a great in-depth look at the pathophysiology and management of the disease processes in veterinary patients.*

DE Holt, G Griffin: Bite wounds in dogs and cats. *Vet Clin North Am Small Anim Pract*. **30**, 2000, 669, *Chapter that reviews the mechanism of injury for bite wounds and provides recommendations for initial stabilization and then definitive managements*.

MM Smith: Flail chest. In LG King (Ed.): *Textbook of respiratory diseases in dogs and cats*. 2004, Saunders, St Louis, *Chapter that provides an excellent overview of the pathophysiology and management of flail chest.*

D Vnuk, B Pirkic, D Maticic, et al.: Feline high rise syndrome: 119 cases (1998-2001). *J Feline Med Surg*. **6**, 2004, 305, *Article that focuses on high-rise syndrome in an urban area; describes the various injuries incurred and evaluates the association between the height of the fall and the injuries sustained.*

* See the CD-ROM for a complete list of references

154 Chapter 154 Abdominal Trauma

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154.1 KEY POINTS

- The extent of abdominal trauma is often not known at the initial evaluation, and extensive diagnostic tests are typically necessary to fully assess the status of a particular patient.
- In a patient with suspected abdominal trauma, more immediately life-threatening injuries (such as thoracic or brain-associated neurologic trauma) should be addressed first.
- Important sequelae to abdominal trauma may include hemoperitoneum/hemoretroperitoneum, uroperitoneum/uroretroperitoneum, bile peritonitis, septic peritonitis, and diaphragmatic or body wall ruptures.
- Although some animals experiencing abdominal trauma can be managed conservatively, surgery is often necessary to correct associated abnormalities.

154.2 INTRODUCTION

Rapid assessment and triage of a dog or cat following abdominal trauma is essential. A history and physical examination will assist in targeting appropriate diagnostic testing and prevent delays in stabilization. The traumatic event is often not witnessed and the full extent of injury to the animal may not be readily apparent. Injury may be confined to the skin and superficial tissues or may be life threatening and involve avulsion or rupture of abdominal organs. Conservative management and observation are indicated in some cases; however, others require immediate surgery and prolonged hospitalization. This chapter will discuss specific causes of abdominal trauma, the secondary effects of such trauma, and the diagnostic and treatment options.

154.3 BLUNT TRAUMA

Although motor vehicle accidents, high-rise falls, and intentional physical injuries are often encountered in a veterinary emergency setting, abdominal trauma does not commonly occur with these events in dogs and cats. When blunt trauma to the abdomen does occur, the severity of the abdominal injury is often not recognized immediately, while other life-threatening injuries are being addressed.

A retrospective study of 600 dogs[1] that were struck with a motor vehicle noted that 5% experienced abdominal trauma (as diagnosed by surgery or necropsy). The liver was the abdominal organ most often damaged (31% of the abdominal organ injuries), with injuries ranging from fissures of the capsule/parenchyma to fragmentation of a hepatic lobe. Other organs that were injured frequently included the urinary bladder, diaphragm, and kidney. Of the 33 dogs that died from their injuries, 8 (24%) had abdominal injury alone and 13 (39%) had both abdominal and thoracic injury. It is important to remember that some dogs and cats may not experience internal abdominal trauma, but may still require aggressive surgical procedures for damage that occurs to the skin or abdominal muscles, especially when a vehicle drives over or drags the animal.

High-rise falls in dogs and cats result in abdominal injuries in 15% and 7% of cases, respectively.[2,3] Dogs falling from a height of greater than three stories are more likely to experience abdominal injury than those falling less than or equal to three stories. Also, dogs that fall accidentally more often experience abdominal and hind limb injury than dogs that purposefully jump from a height.[2] In most studies of dogs and cats, thoracic trauma is diagnosed more commonly than abdominal trauma, perhaps due to the readily apparent respiratory compromise in those patients.

Unfortunately, human abuse of companion animals is another cause of blunt abdominal trauma. In a study investigating nonaccidental injury[4] to animals, internal injury to the abdomen was documented less frequently than superficial injuries or fractures. However, 13 of 217 (6%) dogs in this study experienced rupture of an organ, including spleen, liver, bladder, and kidney. Cats tended to experience abdominal muscle rupture. Kicking of the animal was the cause of the abdominal injury in most cases.

154.4 PENETRATING TRAUMA

Penetrating trauma to the abdomen often results in both superficial and internal injuries. Skin wounds may not reveal the full extent of the injury in deeper tissues. The reported incidence of internal organ injury after penetrating trauma has been reported to be as high as 70%.[5]

Bite wounds can result in both blunt and penetrating trauma. Exploration of superficial wounds is often necessary to fully recognize the extent of any organ damage that has occurred.[6] Wounds that do not penetrate the abdomen still require close surgical exploration, because bacteria from the biting animal's mouth or environment will likely contaminate the wound and result in abscess formation.

When large animals attack smaller animals, the victims may be lifted and shaken. This can result in severe crushing and tearing injury as well as avulsion of internal organs or body wall/ diaphragmatic herniation. The organs most commonly injured from bite wounds included the liver, kidney, diaphragm, and stomach in one study.[5]

Gunshot wounds to the abdomen have been reviewed in several papers.[5,7] Of 84 animals reported in one retrospective study,[7] 14 abdominal injuries were encountered. Animals with abdominal injury also tended to have more cardiovascular compromise on presentation than those without abdominal injury.

Other types of penetrating abdominal wounds include stab wounds and impalement injuries (from sticks or other devices) or following a high-rise fall.[4,5,8] Some of these injuries are self-induced, and others are the result of mistreatment. Either way, early intervention is likely required to maximize the success of treatment.

154.5 DIAGNOSTIC TESTS

154.5.1 Blood work

Blood work may support a diagnosis of intraabdominal trauma; however, it rarely localizes the injury to a specific organ(s). A complete blood count may demonstrate the presence of anemia in a dog or cat that is experiencing a bleed from either a superficial wound or a deep injury (such as organ rupture), although this change is not typically present in the acute setting. The white blood cell count can increase secondary to stress, inflammation, or an infection that may be localized (in abscess form) or systemic (as with sepsis). The platelet count may be decreased from acute blood loss and subsequent consumption during clot formation. In severe cases of abdominal trauma, disseminated intravascular coagulation (DIC) may occur, leading to thrombocytopenia and prolongation of the prothrombin and activated partial thromboplastin times (see Chapter 117, Hypercoagulable States).

Liver enzyme elevations are often noted on the chemistry screen if hepatic trauma has occurred. If the biliary system is ruptured, progressive increases in total bilirubin will be observed. Azotemia and electrolyte disturbances (e.g., hyperkalemia) will occur secondary to urinary tract rupture. Animals with sterile or septic peritonitis or a persistently draining wound may develop hypoproteinemia.

154.5.2 Radiography

Abdominal radiographs are useful in the diagnosis of abdominal pathology, but it is not always possible to identify a specific cause. The presence of intraabdominal gas suggests that abdominal wall penetration or organ perforation has occurred and requires immediate attention. The general loss of serosal detail in the abdomen is suggestive of fluid in the peritoneal space, retroperitoneal space, or both. Animals with traumatic pancreatitis or very young or thin animals may also have poor serosal detail on radiographs.

Fluid in the peritoneal space may originate from a bleeding organ or ruptured vessel, urine from a distal ureteral, bladder, or proximal urethral rupture, bile from a rupture in the biliary system, or a septic exudate due to septic peritonitis. Fluid in the retroperitoneal space is most commonly urine from damage to the kidney or proximal ureter or blood from a great vessel. Subcutaneous emphysema can be seen when gas accumulates in the subcutaneous spaces, with or without abdominal injury.

Diaphragmatic and body wall ruptures are commonly diagnosed with radiographs.[9,10] Both thoracic and abdominal radiographs should be taken in cases of suspected diaphragmatic rupture. Characteristic changes seen on radiographs in animals with diaphragmatic rupture include loss of continuity of the diaphragm, loss of intrathoracic detail (specifically cardiac silhouette), and the presence of gas-filled bowel loops or a mass effect in the thorax. These changes are not always present, and further imaging may be necessary to confirm the diagnosis.

154.5.3 Ultrasonography

Ultrasonography is useful in some cases of abdominal trauma. As with radiographs, ultrasonography can diagnose the presence of air or gas in the abdomen. One study found that abdominal ultrasound correctly revealed a diaphragmatic hernia in 93% of cases.[11] A suspected body wall rupture can be definitively diagnosed with an ultrasound examination, and the organs displaced through the rupture may be assessed.

An ultrasonographic modality that is gaining popularity in veterinary medicine is the focused assessment with sonography for trauma, or FAST, technique.[12] This approach involves quickly looking at the abdomen with two ultrasonographic views (transverse and longitudinal) in four specific areas, “just caudal to the xiphoid process, just cranial to the pelvis, and over the right and left flanks caudal to the ribs at the most gravity-dependent location of the abdomen.”[12] This technique was found useful for detecting abdominal fluid, even when used by veterinarians with minimal ultrasonographic experience.[12]

154.5.4 Additional Imaging

Other imaging modalities employed in cases of abdominal trauma include fluoroscopy and computed tomography (CT) scans. Both are useful in the diagnosis of urinary tract injuries and body wall or diaphragmatic ruptures, and CT scans are used commonly for surgical planning in human patients that have experienced abdominal trauma.[13]

154.5.5 Abdominal Fluid Analysis

When an abdominal effusion is suspected from results of the physical examination, radiographs or ultrasonography, it is important to obtain a sample of the fluid for evaluation (see Chapter 155, Abdominocentesis). Several analyses should be performed on the fluid sample, including hematocrit, total solids, bilirubin, creatinine, potassium, and glucose. Other tests may include carbon dioxide, lactate, amylase, and lipase. In addition, a slide of the sample should be made for cytologic examination.

The presence of red blood cells in an abdominal effusion does not necessarily confirm a hemoperitoneum. With a true hemoperitoneum, red blood cells are usually observed within macrophages, signifying erythrophagocytosis (although this may not be present during the acute stages). Hemosiderin from the broken down red blood cells usually fills the cytoplasm of the involved phagocyte.[14] Alternatively, if the packed cell volume (PCV) of the fluid is increasing or nears that found in the peripheral blood, ongoing hemorrhage should be suspected. Cardiovascular changes are typically present in these animals (i.e., tachycardia, hypotension).

Comparison of the concentrations of creatinine and potassium in an abdominal effusion to the serum levels is a useful indicator of uroperitoneum in both dogs and cats. In cats, mean serum-to-abdominal fluid creatinine ratio and mean serum-to-abdominal fluid potassium ratio have been found to be 1:2 and 1:1.9, respectively, in cases of uroperitoneum.[15] Therefore a cat with a creatinine or potassium concentration in the abdominal effusion that is 2 times (or more) greater than the peripheral blood likely has a uroperitoneum. In dogs, the sensitivity and specificity are both 100% when using a ratio greater than 1.4:1 in comparing abdominal fluid potassium concentration with peripheral blood potassium concentration for the diagnosis of uroperitoneum. Similarly, using abdominal fluid creatinine concentration (as compared with peripheral blood creatinine concentration) was beneficial, in that a ratio of greater than 2:1 was 86% sensitive and 100% specific for the diagnosis of uroperitoneum.[16]

A bilirubin concentration in an abdominal effusion greater than twice that of the peripheral blood is diagnostic for bile leakage.[17] Bile crystals are occasionally evident on cytologic examination. Biliary effusions are often septic, and cytologic evaluation may reveal the presence of bacteria.

The importance of abdominal fluid analysis in the diagnosis of septic peritonitis has been well documented. Cytologic examination is especially important in the diagnosis of septic peritonitis, and the presence of intracellular bacteria confirms the diagnosis (assuming that gastrointestinal contents have not been aspirated). The glucose and lactate concentrations of the peritoneal fluid should also be compared with the respective concentrations in the blood (see Chapter 133, Peritonitis).

154.6 TREATMENT

154.6.1 Initial Assessment

Although abdominal trauma may be life threatening, many animals will have other injuries that warrant more immediate attention. The respiratory and cardiovascular systems should be assessed and stabilized (see Chapters 2 and 65, Patient Triage and Shock Fluids and Fluid Challenge, respectively). Thoracic injuries may require immediate intervention (see Chapter 153, Thoracic Trauma). Obvious bleeding should be controlled as soon as possible. In addition, neurologic dysfunction resulting in seizure activity or signs of intracranial swelling should be a treatment priority (see Chapter 152, Traumatic Brain Injury). Subsequently, an assessment of abdominal, superficial, and orthopedic injuries should be performed.

154.6.2 Hemoperitoneum/Hemoretroperitoneum

The diagnosis of a hemoperitoneum may prove challenging on physical examination. However, many of these animals will present in shock with obvious signs of blood loss and cardiovascular compromise, such as mental depression, pale mucous membranes, prolonged capillary refill time, poor pulse quality, and tachycardia (see Chapter 10, Shock). In the initial treatment of these patients, it is essential to treat hemorrhagic shock and improve perfusion by administering isotonic crystalloids (up to 50 ml/kg in the cat and 90 ml/kg in the dog) and/or synthetic colloids (10 to 20 ml/kg), or both (see Chapter 65, Shock Fluids and Fluid Challenge). “Hypotensive resuscitation”[18] to a mean arterial pressure of 60 mm Hg or systolic blood pressure of 80 mm Hg may prevent excessive bleeding or disruption of clot formation and function. Some animals may also require blood transfusions during the resuscitation period (i.e., whole blood, packed red blood cells, and plasma; see Chapter 66, Transfusion Medicine). Animals that are unresponsive to crystalloid and synthetic colloid fluid resuscitation and have evidence of severe hemorrhage should be given fresh whole blood or packed red blood cells and fresh frozen plasma in an attempt to stabilize the clinical signs of shock, maintain the hematocrit above 25%, and sustain the clotting times within the normal range. Packed red blood cells and fresh frozen plasma are administered at a dosage of 10 to 15 ml/kg and fresh whole blood at a dosage of 20 to 25 ml/kg (a blood type and crossmatch should be performed, if possible).

Following initial stabilization, the decision to manage these cases conservatively (medically) or surgically must be made. External counterpressure with an abdominal bandage has been advocated as a means of stabilizing mean arterial pressure and improving survival.[19] Other immediate management options include internal counterpressure and autotransfusion.[20] The decision to perform surgery is case dependent, but if a patient is not responding to fluid resuscitation efforts, has a rising abdominal PCV, or is obviously continuing to effuse based on ultrasonographic evaluation or physical examination, surgery should be performed.

In a veterinary retrospective study[21] evaluating cases of traumatic hemoperitoneum, the spleen, liver, and kidney were bleeding in 58%, 50%, and 23% of cases, respectively (determined during surgery or necropsy). Of the 28 small animals evaluated in that study, 9 underwent exploratory laparotomy; 4 cases survived to discharge, 2 died, and 3 were euthanized. Discounting the euthanized small animals, the mortality rate for the cases managed surgically was 33%, and the mortality rate for the cases managed medically was 25%. The reasons for choosing surgical versus medical management of these cases were not discussed.

154.6.3 Uroperitoneum/Uroretroperitoneum

A uroperitoneum can occur secondary to injury to the kidneys, ureters, urinary bladder, or urethra.[22] Often, animals experiencing urinary tract trauma will present with hematuria before signs of a uroperitoneum are apparent. In cats, blunt abdominal trauma has been reported to cause 59.1% of the cases of uroperitoneum,[15] and in 84.6% of those cases the source of urine leakage was a ruptured bladder.

Initial stabilization of the patient with a uroperitoneum revolves around the correction of electrolyte abnormalities, especially hyperkalemia. Characteristic electrocardiographic abnormalities noted in cases with hyperkalemia may include tall, tented T waves, absence of P waves, and bradycardia. If not addressed immediately, this can become life threatening. Medical treatment may include the administration of drugs such as calcium gluconate, insulin and/or glucose, bicarbonate, or β-agonist therapy (see Chapters 55 and 133, Potassium Disorders and Peritonitis, respectively).

Definitive surgical treatment for cases of uroperitoneum secondary to renal or ureteral injury is generally necessary for a successful outcome and often results in a ureteronephrectomy. Bladder ruptures often require surgical correction, although small leaks may heal with continuous decompression provided by a urinary catheter and collection system. Surgical correction typically is accomplished by placing sutures over the rupture site. Bladder resection may be necessary if the tissue appears severely damaged. Urethral trauma is treated conservatively in some cases by inserting a urethral catheter or a cystostomy tube, or both. If conservative treatment is unsuccessful, surgical closure of the urethral defect is necessary.

Postoperative supportive care and intensive monitoring are necessary in these animals to ensure a positive outcome. Urine output must be monitored strictly, and resolution of azotemia should be expected if the injury has been managed properly.

154.6.4 Bile Peritonitis

Leakage of bile from the gallbladder or biliary ducts can occur secondary to blunt or penetrating abdominal trauma.[23] It is reportedly more common for blunt trauma to result in ductal rupture than gallbladder rupture, and the site of rupture is typically just distal to the last hepatic duct.[23]

Bile leakage should be addressed surgically as soon as possible. Bile in the peritoneal cavity can cause severe peritonitis, because bile acids are toxic to living tissues. In addition, many biliary effusions are septic and may prove life threatening (see Chapter 133, Peritonitis). Appropriate antibiotic therapy and supportive care are vital.

154.6.5 Septic Peritonitis

Gunshot wounds, bite wounds, and vehicular trauma to the abdomen can result in septic peritonitis either from direct contamination with bacteria or leakage from an abdominal organ. In a retrospective canine study evaluating gunshot and bite wounds to the abdomen, peritonitis was noted in 40% of the dogs with gunshot wounds and 14% of the dogs with bite wounds.[5] Another study in cats found that 8 of 51 cases of septic peritonitis occurred secondary to trauma (gunshot wounds, bite wounds, and motor vehicle trauma).[24]

Animals with septic peritonitis often present in shock and have a palpable abdominal effusion. As with cases of hemoperitoneum, treatment of the cardiovascular and respiratory systems should be instituted first. Fluid resuscitation and antibiotic therapy with broad-spectrum antibiotics are essential (see Chapters 65 and 133, Shock Fluids and Fluid Challenge and Peritonitis, respectively).

When the patient has been stabilized, surgical exploration should be performed, and the inciting cause must be found and eliminated. Septic peritonitis can be managed postoperatively with either open abdominal drainage or primary closure with placement of closed suction drains.[25] If drains are placed, the amount of effusion produced should be monitored and recorded every 2 to 6 hours. Cytologic examination of the fluid should be performed regularly to monitor for recurrence of a septic effusion or a secondary infection.

154.6.6 Diaphragmatic Rupture

Trauma is the most common cause of diaphragmatic ruptures in small animals.[26] Therefore it should be suspected in any dog or cat with respiratory distress following a traumatic event. Furthermore, other obvious clinical lesions may not be present in 48% of cases of traumatic diaphragmatic ruptures.[26]

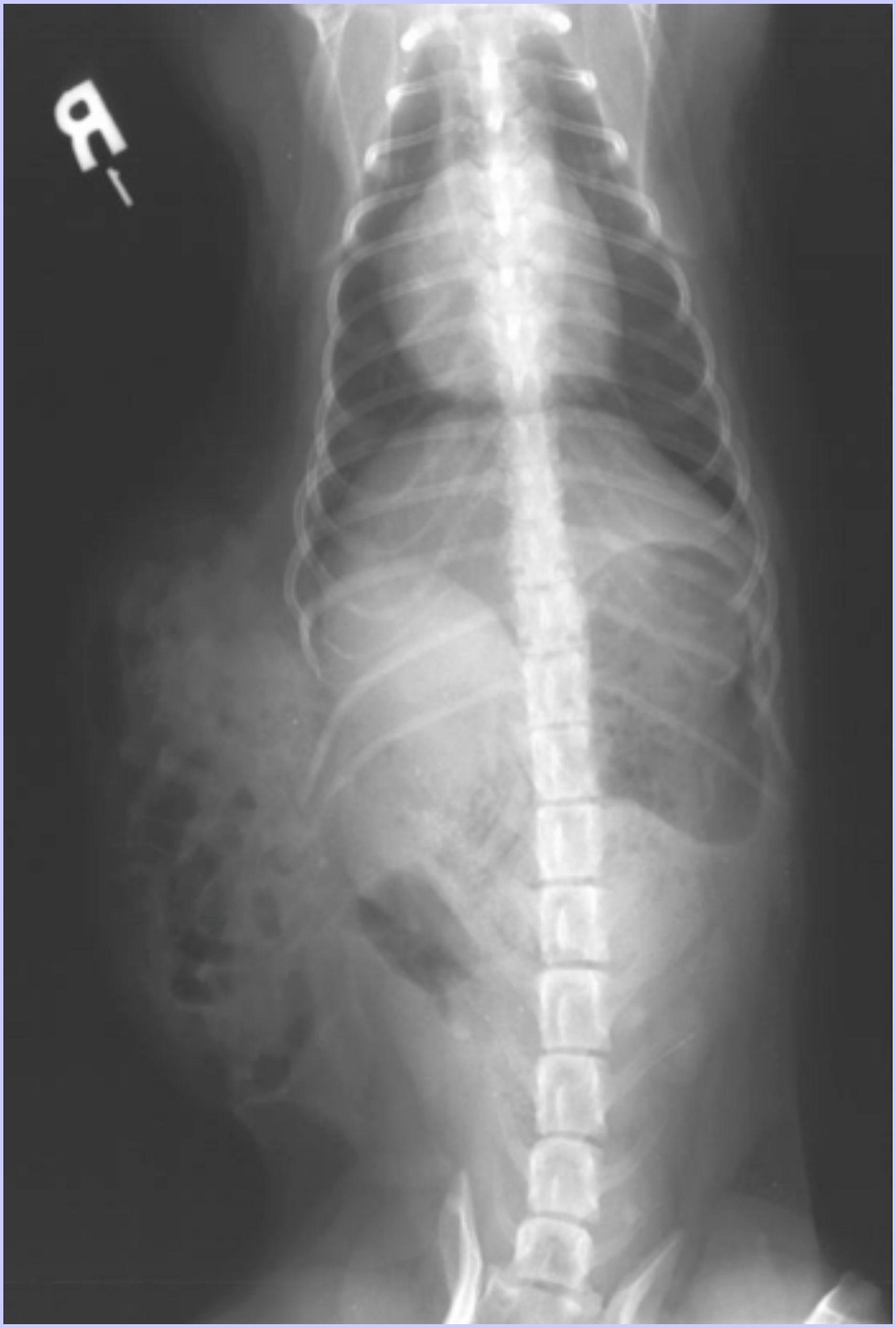
These animals may have clinical signs of shock at presentation, and early stabilization and oxygen therapy should be initiated. Following stabilization, surgery is indicated to repair the rupture (Color Plate 154-1). If the stomach is displaced into the thoracic cavity or respiratory stability is unachievable, surgery is indicated on an emergency basis (see Chapter 30, Pleural Space Disease).

154.6.7 Body Wall Rupture

Abdominal body wall rupture in dogs occurs secondary to bite wounds or vehicular trauma in 86% to 88% of cases.[9,27] These patients should be evaluated carefully for bony trauma as well, because fractures may be the source of the rupture.

Body wall ruptures are generally surgical emergencies, especially if caused by bite wounds. Organs can be trapped in the defect, resulting in strangulation and rapid demise of the patient. Intestines are reportedly displaced through the rupture in as many as 54% of cases,[27] and many require a resection and anastomosis to remove devitalized tissue (Figure 154-1). Other organs commonly displaced include omentum, the liver, and the urinary bladder.[9,27] In one study, 73% of dogs and 80% of cats survived until discharge from the hospital after surgical repair of a body wall rupture.[9]

Figure 154-1 Ventrodorsal radiograph of a dog recently bitten by another dog. Note the presence of abdominal viscera (including intestines) in the subcutaneous space that have passed through a rupture in the right lateral body wall.



154.7 POSTOPERATIVE CARE

Many cases of abdominal trauma require surgery. The postoperative care often entails antibiotic therapy with broad-spectrum coverage until a sensitivity can better target an antibiotic choice in small animals suffering from septic peritonitis, bile peritonitis, and bite wounds. Many patients will be either unable to eat or reluctant to eat for several days after a traumatic event, and an alternative method of nutrition such as a feeding tube or total parenteral nutrition may be indicated. Fluid and blood product supplementation often continue into the postoperative period, as well. Multiple surgeries are often required in animals with concurrent orthopedic injuries.

154.8 SUGGESTED FURTHER READING*

DE Holt, G Griffin: Bite wounds in dogs and cats. *Vet Clin North Am Small Anim Pract*. **30**, 2000, 669, *A good summary of the effects of bite wounds and their treatment*.

MA McLoughlin: Surgical emergencies of the urinary tract. *Vet Clin North Am Small Anim Pract*. **30**, 2000, 581–601, *A review article that discusses the causes of urinary tract trauma and the associated treatment modalities, including some useful diagrams and radiographic examples*.

SP Shaw, EA Rozanski, JE Rush: Traumatic body wall herniation in 36 dogs and cats. *J Am Assoc Hosp Assoc*. **39**, 2003, 35, *A study that evaluates only those patients that received surgical correction of body wall hernias and follows their clinical course from presentation to outcome*.

WO Whitney, CJ Mehlhaff: High-rise syndrome in cats. *J Am Vet Med Assoc*. **191**, 1987, 1399, *A large retrospective study of this syndrome in cats that adequately describes injuries sustained and minimally discusses treatments*.

AJ Worth, RG Machon: Traumatic diaphragmatic herniation: pathophysiology and management. *Comp Cont Educ Pract Vet*. **27**, 2005, 178, *Paper that provides an excellent overview of the pathogenesis, treatment, and prognosis of this condition in companion animals*.

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* See the CD-ROM for a complete list of references

155 Chapter 155 Abdominocentesis

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155.1 KEY POINTS

- Cytology of peritoneal fluid obtained by abdominocentesis may yield a diagnosis and lead to further directed therapy or emergency surgery.
- The focused assessment with sonography for trauma, or FAST, protocol is a rapid and simple technique to detect free abdominal fluid. A needle paracentesis may be successful if directed toward the identified areas.
- A blind-needle paracentesis may yield peritoneal fluid when 5.2 to 6.6 ml/kg of abdominal fluid is present.
- A peritoneal dialysis catheter used for abdominocentesis may detect the presence of 1 to 4.4 ml/kg of abdominal fluid.
- Complications of abdominocentesis include the introduction or spread of infection, laceration of a viscus, and hemorrhage from a punctured vessel or organ.

155.2 INTRODUCTION

Frequent physical examinations are the most informative portion of the diagnostic evaluation of an emergency or intensive care patient with abdominal disease. Assessment of the abdomen should be as complete as time and the patient's condition permit. Increasing abdominal size and progressive pain can be important clues for intraabdominal injury. Consequently, measurements of the abdominal girth at the umbilical level should be made soon after admission. This baseline measurement can be used to assess subsequent significant changes. Abdominal rigidity and tenderness are important clinical signs of peritoneal irritation by blood or intestinal contents. Although physical examination findings can help in the discovery of abdominal disease, they do not further a diagnosis. Samples of peritoneal fluid obtained by abdominocentesis, however, may yield the diagnosis of an abdominal disease process and lead to directed and specific therapy.

155.3 INDICATIONS

Indications for abdominocentesis are (1) radiographic loss of serosal detail, (2) abdominal injury without obvious peritoneal entry wounds, (3) shock, multiple injuries, or signs of abdominal injury after blunt trauma, (4) head or spinal injury precluding reliable abdominal examination, (5) persistent abdominal pain or fluid distention of unknown cause, and (6) postoperative complications possibly caused by leakage from an enterotomy or anastomotic site.[1] Periumbilical ecchymosis (Cullen sign) may indicate hemorrhage in the peritoneum or retroperitoneum. Contraindications to abdominocentesis include coagulopathy, organomegaly, or distention of an abdominal viscus. Intestinal or uterine penetration is rare unless the viscus is dilated and adherent to the abdominal wall.[2] Complications include the introduction or spread of infection, laceration of a viscus, and hemorrhage from a punctured vessel. Following the techniques described below will reduce the risk of complications.

155.4 TECHNIQUE

Abdominocentesis is completed using a single paracentesis or four-quadrant approach. Single paracenteses are done with an open-needle or a closed-needle technique. Ultrasonographic guidance can highlight a smaller accumulation of fluid and allow for a more directed approach for abdominocentesis.

155.4.1 Focused Assessment With Sonography for Trauma

The focused assessment with sonography for trauma, or FAST, protocol was studied in dogs to prove that it is a rapid and simple technique to detect free abdominal fluid in the emergency room by veterinary clinicians with minimal previous ultrasonography experience.[3] This technique scanned four regions in longitudinal and transverse planes of the abdomen with dogs in lateral recumbency. These regions are areas where fluid accumulation commonly occurs: caudal to the xiphoid process, midline over the urinary bladder, and each flank. Of 100 dogs studied within 24 hours of a motor vehicle accident, 45 had free abdominal fluid. A diagnosis was made in all 40 of the dogs that received an abdominocentesis (29 with ultrasonographic guidance); 38 had hemoabdomen, 2 had uroabdomen. Diagnostic peritoneal lavage was not performed on any of the dogs.

155.4.2 Patient Preparation

Patient positioning in left lateral recumbency may be most effective to avoid puncture of the spleen. Restraint may be completed manually or with sedatives and analgesics. Before the abdomen is penetrated, a wide surgical clip and preparation of the site using aseptic technique must be completed along the ventral midline centered at the umbilicus (Color Plate 155-1). If abdominal ultrasonography has revealed a focal area of peritoneal fluid accumulation, a standard aseptic clip and preparation of that location is prudent.

155.4.3 Closed-Needle Abdominocentesis

A closed-needle diagnostic abdominocentesis can be completed using a 20- or 22-gauge needle placed on an extension set that is attached to a 6- or 12-cc syringe. Local anesthetic infusion of 2% lidocaine may be used at the abdominocentesis site. Penetration of the abdominal cavity can be completed in the right cranial quadrant caudal to the edges of the liver, because peritoneal fluid is gravity dependent and the falciform fat may extend along midline to the umbilicus. Gently insert the needle completely at this site and avoid further movement of the needle tip to prevent laceration of internal structures. Withdraw the peritoneal fluid and observe for clots if the fluid is hemorrhagic. Fluid within the abdominal cavity should not clot; hemorrhagic fluid obtained from puncture of the spleen, liver, or any vessel will clot readily. If the abdominal fluid clots, remove the needle and attempt abdominocentesis in another location. Cytologic and biochemical analysis and culture of the abdominal fluid should be completed immediately after removal.

A closed-needle abdominocentesis may also be used for therapeutic removal of peritoneal fluid. Therapeutic removal of large volumes of fluid may be indicated if the abdominal distention impairs diaphragmatic motion, increases abdominal pressure impeding blood flow to the visceral organs, or causes pain. To maintain a closed system, a three-way stopcock can be placed between the syringe and extension set. Another extension set placed on the stopcock can be directed into a bowl or graduated cylinder. Free gas should not be evident on radiographs after a closed-needle abdominocentesis.

155.4.4 Open-Needle Abdominocentesis

An open-needle abdominocentesis is completed in a similar fashion except that the needle, alone, is inserted into the peritoneal cavity. Fluid from the peritoneum is allowed to flow freely through the needle into a container or a sample submission tube. Rotation of the hub of the needle may facilitate flow. This technique helps prevent occlusion with or aspiration of omentum or intestinal viscera. False negative results are more likely to occur if suction is applied.[4] Free gas on radiographs is possible after this procedure.

155.4.5 Four-Quadrant Abdominocentesis

A modification of the open-needle technique is the four-quadrant abdominocentesis. Instead of one open needle, four open needles are placed simultaneously, one in each quadrant surrounding the umbilicus (see Color Plate 155-1). Gravity dependency or changes in transabdominal pressure between the needles may increase the likelihood of obtaining fluid. One study in dogs showed that fluid was obtained in 78 of 100 needle paracenteses when 5.2 to 6.6 ml/kg (ml of abdominal fluid per kg of body weight) was present.[5]

155.4.6 Alternatives to Needles for Abdominocentesis

A peritoneal dialysis catheter used for abdominocentesis can detect 1 to 4.4 ml/kg.[6] A larger diameter and multiple side holes make this apparatus more reliable for detecting smaller volumes of peritoneal fluid compared with a standard needle or catheter (see Chapter 156, Diagnostic Peritoneal Lavage).

A 14- or 16-gauge over-the-needle catheter with manually created fenestrations placed using a No. 10 scalpel blade can increase the surface area for drainage (Color Plate 155-2, *A*). Complete occlusion by the omentum or bowel is less likely and may increase the yield of peritoneal fluid. It is important to make small, smooth fenestrations. Do not place them opposite each other on the catheter or place too many; this will weaken the integrity of the catheter (Color Plate 155-2, *B*). If the catheter is weakened or the fenestrations are not smooth, a portion of the catheter may break and remain in the subcutaneous tissue or intraabdominal space when removed from the abdomen. Once the stylet is removed, do not replace it in the catheter. Despite these caveats, the use of a fenestrated catheter increases the likelihood of fluid collection compared with needle abdominocentesis alone.[7]

155.5 ABDOMINAL FLUID ANALYSIS

Packed cell volume (PCV) and creatinine, glucose, and blood urea nitrogen (BUN) levels should be measured from the peritoneal fluid sample. Potassium and lactate are other biochemical markers that can be tested to add diagnostic value to the fluid sample. If the PCV of the peritoneal fluid exceeds the peripheral PCV, it is suggestive of parenchymal organ laceration or large vascular disruption. Hemodilution with urine may cause a decreased PCV of abdominal fluid in patients with both abdominal hemorrhage and urologic injury. Uroabdomen can be diagnosed from simultaneous measurement of creatinine and potassium in both the abdominal fluid and peripheral blood. Elevation of potassium in the abdominal fluid compared with that of peripheral blood (greater than 1.4:1) suggests urologic injury.[8] Rapid assessment and comparison of the BUN in abdominal fluid and peripheral blood can be completed using reagent strip technology. However, BUN can readily equilibrate across the peritoneal lining and is less reliable for the diagnosis of uroabdomen. Because of its high molecular weight, a creatinine concentration in the abdominal fluid higher than twice that of peripheral blood is highly suggestive of free urine in the abdominal cavity.[9]

Cytologic analysis and culture of abdominal fluid with sensitivity testing should be carried out. Emergency cytologic analysis often assists the clinician in initiating appropriate therapy. In many cases, the decision for medical versus surgical therapy can be readily apparent before receiving the official clinical pathologic review. The emergency clinician or intensivist should examine the gross appearance of the fluid. An abdominal fluid sample that is completely clear and colorless makes the diagnosis of peritonitis, severe intraabdominal injury or perforation, and leakage from the gastrointestinal tract less likely.[4] Fluid that appears opaque, cloudy, or flocculent should be examined immediately.

A direct smear that has been dried and stained appropriately can be examined at low power for large particulate material such as plant material or crystals. High-power magnification is used to identify bacteria, fungi, and blood cells. Intracellular bacteria (with or without extracellular bacteria) and degenerate neutrophils characterize a septic effusion. One study[10] showed these parameters were 100% accurate for the diagnosis of septic peritonitis. Surgical intervention should be considered and undertaken immediately if this is found, often before confirmation by a reference laboratory. Surgery is not necessarily indicated when only extracellular bacteria are found in the fluid sample. Glucose and lactate measurements on peritoneal fluid can also aid in the diagnosis of septic peritonitis. In one prospective analysis of 18 dogs with septic effusion, peritoneal fluid glucose concentration was always lower than the blood glucose concentration.[11] A blood–to–peritoneal fluid glucose difference greater than 20 mg/dl was 100% sensitive and 100% specific for the diagnosis of septic peritoneal effusion in dogs.

With gallbladder or common bile duct injury, icterus may be delayed. A dark green to black or dark amber color of peritoneal fluid suggests the presence of bile pigments. Peritoneal fluid can be analyzed for total bilirubin. If the abdominal fluid bilirubin is significantly greater than peripheral bilirubin, then bile peritonitis is present.

Abdominal disease and the associated abdominal fluid can change rapidly. As a result these patients require frequent reassessments of their physical status and diligent critical care monitoring. Repeated abdominocentesis may play a role in clinical decision making.

155.6 CONCLUSION

Physical examination findings and diagnostic studies are required to decide when acute abdominal disease should be explored surgically versus managed medically. Blunt abdominal trauma cases are a challenge to diagnose, because the clinical manifestations may be delayed for hours or days. Abdominocentesis is a valuable tool to obtain a sample for laboratory and cytologic analysis in the emergency room or intensive care unit.

155.7 SUGGESTED FURTHER READING*

SR Boysen, EA Rozanski, AS Tidwell, et al.: Evaluation of a focused assessment with sonography for trauma protocol to detect free abdominal fluid in dogs involved in motor vehicle accidents. *J Am Vet Med Assoc*. **225**, 2004, 1198, *An interesting, prospective study that reports the focused assessment with sonography for trauma protocol as adapted from human medicine for rapid identification of free peritoneal fluid within 24 hours after blunt trauma in dogs.*

J Giacobine, VE Siler: Evaluation of diagnostic abdominal paracentesis with experimental and clinical studies. *Surg Gynecol Obstet*. **110**, 1960, 676, *A seminal article that reports the use of needle abdominal paracentesis in dogs, including false-positive rates and peritoneal fluid volumes detected with this technique.*

RJ Kolata: Diagnostic abdominal paracentesis and lavage: experimental and clinical evaluations in the dog. *J Am Vet Med Assoc*. **168**, 1976, 697, *A prospective, descriptive article evaluating the experimental and clinical use of a peritoneal dialysis catheter for abdominocentesis and diagnostic peritoneal lavage in dogs*.

C Schmiedt, KM Tobias, CM Otto: Evaluation of abdominal fluid:peripheral blood creatinine and potassium ratios for diagnosis of uroperitoneum in dogs. *J Vet Emerg Crit Care*. **11**, 2001, 275, *An interesting article that prospectively establishes the abdominal fluid–to–peripheral blood creatinine ratios used for diagnosis of uroperitoneum in dogs*.

* See the CD-ROM for a complete list of references

156 Chapter 156 Diagnostic Peritoneal Lavage

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156.1 KEY POINTS

- Diagnostic peritoneal lavage (DPL) is performed when intraabdominal injury is suspected and when alternative diagnostic methods such as sonography are unavailable or the patient's condition does not allow other diagnostic techniques or imaging to be performed.
- DPL is complementary to abdominocentesis.
- DPL does not reliably exclude significant injuries to retroperitoneal structures.
- Significant hemorrhage is present if the packed cell volume (PCV) of the peritoneal fluid exceeds 5%.
- Creatinine in the abdominal fluid more than twice that of peripheral blood is highly suggestive of free urine in the abdominal cavity.

156.2 INTRODUCTION

Abdominal disease can have life-threatening consequences, and in some cases surgical intervention is essential. Determining when surgery is indicated can be challenging, because abdominal clinical signs are commonly vague and nonspecific. Blunt trauma to the abdomen is a major component of traumatic injury and can be deadly. It can occur as a consequence of falls, motor vehicle accidents, or severe blows to the abdomen. Many other causes for an acute condition of the abdomen may warrant further diagnosis with the aid of abdominal fluid cytology.

When there is 5.2 to 6.6 ml of abdominal fluid per kg of body weight,[1] abdominocentesis is a valuable diagnostic procedure. When there is insufficient fluid for abdominocentesis, diagnostic peritoneal lavage DPL can provide a fluid sample for analysis. The cytologic and biochemical information obtained from a DPL helps determine whether an intraabdominal injury exists and whether surgery is required.

156.3 INDICATIONS

DPL should be considered when a diagnostic sample was not obtained by abdominocentesis. Specific indications for a diagnostic peritoneal lavage are (1) an acute condition of the abdomen, (2) penetrating or blunt abdominal trauma, (3) shock despite maximal fluid resuscitation, (4) central nervous system disease precluding reliable abdominal examination, (5) persistent abdominal pain of unknown cause, and (6) to assess postoperative dehiscence of an enterotomy or anastomotic site.[2,3] Contraindications include coagulopathy, organomegaly, and distention of an abdominal viscus. Complications include the introduction or spread of infection, laceration of a viscus, and hemorrhage from a punctured vessel, although the complication rate is quite low. DPL does not reliably exclude significant injuries to retroperitoneal structures.

Diagnostic peritoneal lavage is performed when alternative diagnostic methods such as sonography are unavailable or when the patient's condition does not allow other diagnostic tests or imaging to be performed. The focused assessment with sonography for trauma (FAST) protocol was studied in dogs to prove that it is a rapid and simple technique to detect free abdominal fluid in the emergency room by veterinary clinicians with minimal ultrasonography experience.[4] Using this technique, the operators scanned four regions in longitudinal and transverse planes of the abdomen with dogs in lateral recumbency. These regions are caudal to the xiphoid process, midline over the urinary bladder, and each flank. FAST was completed within a median time of 6 minutes. An accurate cytologic diagnosis was made in all dogs that received needle abdominocentesis. DPL was not performed on any of the dogs.

156.4 TECHNIQUE

Crowe and Crane described an open technique for DPL.[5] A 1-cm incision is made carefully in the abdomen for direct visualization of catheter insertion into the peritoneal cavity. Careful hemostasis must be maintained to prevent false-positive results on fluid analysis. A closed technique has also been described using a catheter with an inner stylet that is rotated gently to penetrate the fascia and peritoneum.[1] A modification of the closed technique is presented.[6,7]

156.4.1 Supplies

DPL is performed with a large-diameter catheter with multiple holes. Commercial peritoneal dialysis catheters work well, but over-the-needle catheters can be fenestrated and used with good results. Use of a peritoneal dialysis catheter for abdominocentesis alone, without lavage, has been shown to detect 1 to 4.4 ml/kg of free abdominal fluid.[8] The larger diameter and multiple side holes of a peritoneal dialysis catheter make occlusion with omentum or bowel less likely. A 14-gauge or 16-gauge over-the-needle catheter with fenestrations placed manually using a No. 10 scalpel blade can increase the surface area for drainage (see Chapter 155, Abdominocentesis, and Color Plate 155-2, *A*). Fenestrations should be small and smooth. Fenestrations should not be too numerous or placed opposite each other on the catheter; this will weaken the integrity of the catheter (see Chapter 155, Abdominocentesis, and Color Plate 155-2, *B*). If the catheter is weakened or the fenestrations are not smooth, a portion of the catheter may break and remain in the subcutaneous tissue or intraabdominal space when removed from the abdomen.

156.4.1.1 Box 156-1 Supplies Needed for Diagnostic Peritoneal Lavage

- Clippers
- Surgical antiseptic scrub
- Peritoneal dialysis catheter or 14- or 16-gauge over-the-needle catheter
- No. 10 scalpel blade
- 2% Lidocaine
- No. 11 scalpel blade
- Fluid administration set
- Warm 0.9% saline, 22 ml/kg

Other supplies needed for a diagnostic peritoneal lavage include local anesthetic, a No. 11 scalpel blade, a fluid administration set, and sterile warm 0.9% sodium chloride for infusion (Box 156-1).

156.4.2 Patient Preparation

Left lateral recumbency may be the best position for prevention of splenic puncture. Restraint may be completed manually or with sedatives and analgesics. Before penetration of the abdomen, a wide surgical clip and preparation of the site using aseptic technique must be completed along the ventral midline, centered about the umbilicus. Local infiltration of 2% lidocaine should be performed at the puncture site either at the umbilicus or 2 to 3 cm lateral to it to avoid the falciform fat.

156.4.3 Catheter Placement

A small stab incision is made in the skin with the No. 11 scalpel blade at the site of local anesthetic infiltration. The commercial dialysis catheter is introduced through the incision completely into the abdomen. Slow, gentle rotation of the closed-end dialysis catheter is needed to overcome considerable resistance from fascia and the linea alba. If using a fenestrated over-the-needle catheter, advance the catheter completely off the stylet once the tip has penetrated the peritoneal cavity. A syringe may be attached to the catheter at this point.

If no peritoneal fluid is obtained, saline is infused into the abdomen through the catheter. Infuse 22 ml/kg warm, sterile 0.9% sodium chloride by gravity through the drip set attached to the catheter. Gently massage the abdomen or roll the patient without dislodging the catheter to distribute the saline throughout the abdomen. Either attach a syringe and gently aspirate fluid from the catheter or allow gravity to fill the drip set and fluid bag. Large volumes of fluid are generally not obtained because of the wide dispersion throughout the abdomen. Any amount retrieved should be submitted for biochemical and cytologic evaluation, including culture and sensitivity testing.

156.5 FLUID ANALYSIS

Peritoneal lavage fluid should be examined for color, packed cell volume (PCV), and white blood cell count. Fluid that appears opaque, cloudy, or flocculent should be examined immediately. Fluid from a patient with peritonitis is often cloudy (i.e., highly cellular) but may appear less so with dilution from a peritoneal lavage. An abdominal fluid sample that appears grossly clear and colorless should still be submitted to a reference laboratory for cytologic analysis. A fluid sample should be kept for culture and sensitivity testing.

Cytologic characteristics of the white blood cells are more meaningful than absolute cell counts because of the dilutional consequences of a peritoneal lavage.[6,9] In a study comparing preoperative and postoperative DPL samples, recent surgery increased the white blood cell counts from normal (1000 cells/mm^3) to usually less than 10,000 cells/mm^3.[10] Elevations in the peritoneal white blood cell count in response to sepsis occur over variable periods[1] that overlap these normal ranges. Intracellular bacteria (with or without extracellular bacteria) along with an increased number of degenerate neutrophils characterize a septic effusion. Surgical intervention should be undertaken immediately if this is found, often before confirmation by a reference laboratory. It is important to note that the presence of extracellular bacteria in the absence of intracellular bacteria is not diagnostic of septic peritonitis and hence not an indication for surgery.

Because of dilution, the PCV of the DPL fluid cannot be compared directly with the peripheral blood PCV. It has been reported that a PCV of the DPL fluid of greater than 5% indicates significant hemorrhage.[6] Serial assessments of the abdominal fluid with increasing PCVs may more clearly define continuing hemorrhage.

Creatinine and potassium elevations in the lavage fluid are more difficult to interpret because of the dilutional effects of the infusate. Excretory urography, retrograde contrast cystourethrography, or surgical intervention may be indicated.

With gallbladder or common bile duct injury, icterus may be delayed. Some of the peritoneal fluid should be submitted for analysis of total bilirubin. A dark green to black color suggests bile pigments within the fluid. If the abdominal fluid bilirubin is disproportionately greater than peripheral bilirubin, an exploratory laparotomy is indicated.

156.6 CONCLUSION

Injury to abdominal viscera must be excluded in all victims of abdominal trauma. Patients requiring intensive care may also develop progressive abdominal disease. Physical examination remains the initial step in diagnosis but has limited utility under some circumstances. The specific tests selected are based on the clinical stability of the patient, the ability to conduct a reliable physical examination, and the clinician's access to diagnostic modalities. Diagnostic peritoneal lavage is indicated in a patient that has significant abdominal injury but no diagnostic sample was identified by FAST or routine abdominal ultrasonography or obtained by abdominocentesis.

DPL does not reliably exclude significant injuries to retroperitoneal structures. Kane and others[11] performed computed tomography following DPL in 44 hemodynamically stable human patients that had sustained blunt trauma. In 16 patients, computed tomography revealed significant intraabdominal or retroperitoneal injuries not diagnosed by DPL. Moreover, the findings of computed tomography resulted in a modification to the original management plan in 58% of the patients. There are no similar studies in veterinary medicine.

156.7 SUGGESTED FURTHER READING*

DE Bjorling, KS Latimer, CA Rawlings, et al.: Diagnostic peritoneal lavage before and after abdominal surgery in dogs. *Am J Vet Res*. **44**, 1983, 816, *A study that measured complete blood counts and peritoneal lavage fluid 2 days before and 2 days after abdominal surgery. Dialysis catheter insertion in a right paramedian location resulted in more contamination with blood than when the catheter was inserted on the abdominal midline*.

SR Boysen, EA Rozanski, AS Tidwell, et al.: Evaluation of a focused assessment with sonography for trauma protocol to detect free abdominal fluid in dogs involved in motor vehicle accidents. *J Am Vet Med Assoc*. **225**, 2004, 1198, *An interesting, prospective study reporting the FAST protocol as adapted from human medicine for rapid identification of free peritoneal fluid within 24 hours after blunt trauma in dogs*.

J Giacobine, VE Siler: Evaluation of diagnostic abdominal paracentesis with experimental and clinical studies. *Surg Gynecol Obstet*. **110**, 1960, 676, *A seminal article that reports the use of needle abdominal paracentesis in dogs, including false-positive rates and peritoneal fluid volumes detected with this technique*.

RJ Kolata: Diagnostic abdominal paracentesis and lavage: experimental and clinical evaluations in the dog. *J Am Vet Med Assoc*. **168**, 1976, 697, *A prospective, descriptive article that evaluates the experimental and clinical use of a peritoneal dialysis catheter for abdominocentesis and diagnostic peritoneal lavage in dogs*.

* See the CD-ROM for a complete list of references

157 Chapter 157 Wound Management

Caroline K. Garzotto, VMD, DACVS

157.1 KEY POINTS

- The patient should always be stabilized and assessed for internal trauma (radiographs of chest and abdomen) before treating external wounds.
- In the first aid care of wounds, it is important to keep the wound moist, clean, and covered until definitive treatment can be done.
- Open wounds containing penetrating foreign bodies or projecting bone should not be manipulated until the patient has been stabilized.
- Once the patient is stable, all wounds should be cleaned and debrided, even if the animal will eventually be transferred to a surgical specialist. Surgical exploration is indicated for all penetrating wounds.
- Most wounds can be managed successfully with appropriate technique, close follow-up, cooperative owners, and minimal materials.
- The diagnosis and prognosis for full return to function should be discussed with the owner as soon as possible. Discuss the patient's treatment regimen (e.g., daily bandage changes) and give an estimate for the cost of treatment in the short and long term.

157.2 INTRODUCTION

Most traumatic wounds seen in the small animal veterinary patient include bite wounds, abrasions or shearing injuries resulting from motor vehicle trauma, degloving, lacerations, and punctures. Wounds can also result from decubitus ulcers in the recumbent animal secondary to poor nursing care, or wounds can appear in postoperative surgical incisions that dehisce or become infected.

157.3 WOUND HEALING PRINCIPLES

157.3.1 Wound Classification

Wounds are classified based on degree of contamination as follows:[1-3]

- *Clean:* Atraumatic, surgically created under aseptic conditions (e.g., incisions)
- *Clean contaminated:* Minor break in aseptic surgical technique (e.g., controlled entry into the gastrointestinal, urogenital, or respiratory tracts) in which the contamination is minimal and easily removed
- *Contaminated:* Recent wound related to trauma with bacterial contamination from street, soil, or oral cavity (e.g., abrasion or shearing wound); can also be a surgical wound with major breaks in asepsis (e.g., spillage from the gastrointestinal or urogenital tracts)

- *Dirty or infected:* Old traumatic wound with exudate or obvious infection (e.g., abscess in a bite wound, puncture wound, or traumatic wound with retained devitalized tissue); contains more than 10^5 organisms per gram of tissue

If a wound is associated with a broken bone, this is called an *open fracture,* and these can be classified as follows[4]:

- *Grade I:* Small break in the skin caused by the bone penetrating through
- *Grade II:* Soft tissue trauma contiguous with the fracture, often caused by external trauma (e.g., bite wound, low-velocity gunshot injuries)

- *Grade III:* Extensive soft-tissue injury, commonly in addition to a high degree of comminution of the bone (e.g., distal extremity shearing wounds, high-velocity gunshot injuries)

Although definitive repair of an open fracture should be done as soon as possible for patient comfort, initial care of the soft tissues should not be delayed if a surgeon is not immediately available or if the patient is not stable enough to undergo general anesthesia for several hours. Any exposed bone should be covered with sterile lubricating jelly and a sterile bandage but should not be pushed back below the skin surface because this can cause deeper contamination of the wound or further injury to the tissues. Similar guidelines exist for wounds with penetrating foreign bodies such as arrows, large wooden splinters, or knives. The foreign body may be tamponading a large vessel, and removal may lead to severe hemorrhage. These objects should be removed only under controlled surgical conditions.

Other wound classifications describe the length of time that the wound has been open because this relates to how quickly bacteria can multiply in a wound. Although this is important to know, it is not as vital as assessing the patient and the wound directly. It is more important to understand the local and systemic defenses of the patient and the types and virulence of bacteria that may be present in the wound so that appropriate treatment can be initiated.[1]

157.3.2 Phases of Healing

A basic understanding of the phases of wound healing gives the clinician an idea of how long it will take for a wound to improve in appearance and for making wound management decisions. Wound healing can be described in four phases: (1) inflammation, (2) debridement, (3) repair/proliferation, and (4) maturation.[1] The phases overlap and the transitions are not visible to the naked eye.

The inflammatory phase occurs during the first 5 days after injury. Immediately after trauma there is hemorrhage caused by disruption of blood vessels, and then vasoconstriction and platelet aggregation limits the bleeding. Vasodilation follows within 5 to 10 minutes, allowing fibrinogen and clotting elements to leak from the plasma into the wound to form a clot and eventually a scab. The clot serves as scaffolding for invading cells such as neutrophils, monocytes, fibroblasts, and endothelial cells. Also contained in the plasma are inflammatory mediators (cytokines) such as histamine, prostaglandins, leukotrienes, complement, and growth factors.

The debridement phase occurs almost simultaneously with the inflammatory phase. It is marked by the entry of white blood cells into the wound. Neutrophils are the first to appear in the wound approximately 6 hours after injury. They remove extracellular debris via enzyme release and phagocytosis. Monocytes appear approximately

12 hours after trauma, and they become macrophages within 24 to 48 hours. The monocytes stimulate fibroblastic activity, collagen synthesis, and angiogenesis. Macrophages remove necrotic tissue, bacteria, and foreign material.

The repair phase, also called the *proliferative phase,* [5,6] begins 3 to 5 days after injury and lasts about 2 to 4 weeks. This is the most dramatic healing phase and is characterized by angiogenesis, granulation tissue formation, and epithelialization. Fibroblasts proliferate and start synthesizing collagen, and then capillary beds grow in to form granulation tissue. Granulation tissue provides a surface for epithelialization and is a source of myofibroblasts that play a role in wound contraction. New epithelium is visible 4 to 5 days after injury and occurs faster in a moist environment.[1] Wound contraction is first noticeable by 5 to 9 days after injury and continues into the maturation phase.[6]

Finally, the maturation phase occurs once adequate collagen deposition is present and is marked by wound contraction and remodeling of the collagen fiber bundles. It starts at about 17 to 20 days after injury and may continue for several years. Healed wounds are never as strong as the normal tissue; a scar is only about 80% as strong as the original tissue.[6]

157.4 INITIAL PATIENT ASSESSMENT

Before handling the patient, the clinician and patient should be protected by the use of examination gloves. Initial stabilization of the patient should address oxygenation and circulatory requirements (see Chapter 2, Patient Triage). Intravenous catheter placement, fluid therapy, and supplemental oxygen may be required for the severely traumatized patients or patients in shock (see Chapters 19 and 65, Oxyen Therapy and Shock Fluids and Fluid Challenge, respectively). A complete blood count, biochemical analysis, urinalysis, and venous or arterial blood gas analysis should be performed on admission.

Direct pressure should be applied to any bleeding wounds. If bleeding cannot be controlled by direct pressure, surgical intervention is required. Bleeding of appendages can be controlled with tourniquets by using a pneumatic blood pressure cuff inflated to 200 mm Hg for not more than 1 hour.[7]It is important to remember that bite wounds commonly result from the penetration of both the upper and lower teeth. If bite marks are seen only on one side of the limb or trunk, then the other side should be shaved to search for the corresponding wounds. Wounds should be kept clean and moist and protected immediately from the hospital environment. A sterile, water-soluble lubricant and saline soaked sponges can be applied initially to the wounds and then covered with a sterile towel and soft padded bandage if the patient must be moved. It is important that the damaged tissue remain moist because desiccation impairs wound healing.

If the animal has wounds associated with trauma, radiographs are indicated to assess for other more immediate, life-threatening injuries. These radiographs might include views of the spine, chest, abdomen, and pelvic region, in addition to appendages, if there is suspicion of a fracture. Blunt trauma, such as motor vehicle trauma or falling from heights, warrants chest and abdominal radiographs to assess for pulmonary contusions, pneumothorax or hemothorax, diaphragmatic hernia, and peritoneal effusion secondary to blood or urinary tract trauma. Cursory abdominal ultrasonography may also assist in detecting free fluid within the thoracic or abdominal cavity. A thorough neurologic assessment is also important, to rule out spinal or neurologic injury. Assessment of perfusion and sensation to the digits is important when severe trauma to peripheral blood supply and nerves might prohibit a successful outcome.

157.5 DEBRIDEMENT AND LAVAGE

Once the patient has been thoroughly examined, stabilized, and all diagnostic tests performed, and if sedation or anesthesia can be administered safely, initial assessment and debridement of the wound should be done. The primary goal in the management of all wounds is to create a healthy wound bed with a good blood supply that is free of necrotic tissue and infection to promote healing.[5] Most wounds will require daily debridement and bandage changes, and the clinician should not be discouraged if the wound cannot be closed initially. The following summarizes the steps for daily wound evaluation:

1 Assess need for or response to antibiotic therapy.

2 Debride, removing necrotic tissue, and then lavage the wound.

3 Determine if the wound can be closed.

4 Protect the wound with a bandage, Elizabethan collar, or both.

Initial debridement will require general anesthesia, local anesthesia, or neuroleptanalgesia. For future wound evaluations, the patient may require only sedation or analgesia and restraint, if surgical debridement is minimal. Local anesthetics are ideal for the patient that is not stable enough for general anesthesia and has injuries to the limbs. In these cases, wounds in the hind limb area can be debrided using epidural analgesia (see Chapter 164, Analgesia and Constant Rate Infusions) and forelimb wounds can be debrided using a brachial plexus block.[8]

Sterile lubricating jelly should be applied to the exposed wound to protect it from further contamination, and a wide area of fur clipped from the skin around the wound. Gross dirt from the skin around the wound should be cleaned by applying surgical scrub solution (chlorhexidine or povidone-iodine) to unbroken skin, but *not* to the surface of the wound because these solutions are damaging to exposed tissues.

Debridement should be done using aseptic technique: use sterile gloves, sterile gown, cap and mask, and the wound should be draped with sterile towels or water-impermeable drapes. At the time of initial assessment and subsequent bandage changes, necrotic tissue should be excised. All bite wounds should be explored, even if they look minor, because teeth exert a macerating or crushing force that can damage tissues deep below the skin surface (Color Plate 157-1). The hole around the bite wound should be trimmed and then tented up to evaluate the subcutaneous tissues. A probe, such as a mosquito or Kelly forceps, can be used to assess for dead space or pockets under the skin that could form hematomas, seromas, and abscesses.

Obviously necrotic tissue (black, green, or gray) is removed first. In areas that have ample skin for closure, initial trimming of skin can be done more aggressively. In areas such as the distal limbs, trimming of skin should be done conservatively, and time can be given to let questionable tissues “declare” themselves (Color Plate 157-2). Bone, tendons, nerves, and vessels are preserved as much as possible unless segments of these vital structures are completely separated from the tissue and obviously nonviable.

The wound can be lavaged with a variety of solutions. In wounds heavily contaminated with road dirt or soil, lukewarm tap water with a spray nozzle may be the most efficient way to remove debris.[1] Maggots should be removed from severely necrotic wounds manually or with aggressive flushing. Chlorhexidine and povidone-iodine can be used in dilute form (chlorhexidine 0.05% solution: 1 part chlorhexidine 2% + 40 parts sterile water; povidone-iodine 1% solution: 1 part povidone-iodine 10% + 9 parts sterile saline) as initial lavage in contaminated and infected wounds because of their wide spectrum of antimicrobial activity. Povidone-iodine is more irritating to tissues, toxic to cells needed for wound healing, and inactivated by organic debris,[1] so it may not be the ideal lavage solution. Lactated Ringer's or normal saline are the most commonly used lavage solutions. An in vitro study demonstrated that normal saline and tap water cause mild and severe cytotoxic effects on fibroblasts, respectively, whereas lactated Ringer's solution did not cause significant fibroblast injury.[9]

Lavage is performed by flushing with a bulb syringe or a 60-ml syringe with an 18-gauge needle. For efficiency, the syringe and needle setup can be connected to a three-way stopcock and an intravenous fluid bag to facilitate refilling.

Sugar has a bactericidal effect. Its osmotic action draws macrophages to the wound and accelerates sloughing of devitalized tissue.[10] It is especially advantageous because it is effective and economical for large wounds. Indications include degloving and shearing injuries, infected wounds (*Streptococcus, Escherichia coli,* and *Pseudomonas* spp), burns, and other wounds that require further debridement. The wound is first debrided and lavaged. The area is then patted dry with a sterile towel before applying a coating (up to 1 cm thick) of granulated sugar. A wet-to-dry dressing is applied and changed daily, or more frequently if strike-through occurs. Sugar application is stopped when epithelialization begins.

157.6 WOUND CLOSURE

The decision on when and how to close a wound depends on the cleanliness and extent of the wound.

Clean, fresh wounds, small, contaminated wounds, or even infected wounds that can be excised completely can be closed primarily. Monofilament absorbable suture should be used in subcutaneous tissue and muscle, and nonabsorbable suture should be used on the skin. Avoid tight sutures and tension on the suture line.

Closure should be delayed for contaminated wounds or large wounds with questionable viability. Closure can be performed when a healthy granulation bed is present, which occurs during the repair phase of healing. Healthy granulation tissue should be pink, smooth, or slightly bumpy, cover the entire wound, and should bleed on the cut surface or when an adhered dressing is removed. If in doubt, the wound should be treated as an open infected wound until the granulation bed improves.

Delayed primary closure of a wound is performed 2 to 5 days after the injury. Secondary closure of a wound is defined as closure of a wound 5 or more days after wounding and is usually selected for wounds that were initially classified as dirty (Color Plate 157-3). If the wound is at least 5 days old, granulation tissue and epithelialized skin edges may need to be excised to allow closure.[2] If the wound is too large to be closed, the clinician should consider a skin graft or flap or closure by second-intention healing. Second-intention healing occurs over a healthy granulation bed by the processes of wound contraction and epithelialization, which continue until the two epithelialized edges of the wound meet. Second-intention healing, even of very large wounds, can often be successful and does not require anything more than diligent bandaging.

157.6.1 Exposed Bone

Exposed bone is prone to slow healing and must be covered with a granulation bed before skin graft or flap application. Injuries with exposed bone are seen most often with carpal or tarsal shearing injuries caused by motor vehicle trauma. Exposed bone in most cases is eventually covered by advancing granulation tissue from surrounding healthy soft tissues. 678 679

Bone perforation can enhance wound healing by encouraging growth of granulation tissue over the exposed bone.[1,5,11] Once the wound has entered the repair phase, a Jacob's chuck and 0.045- to 0.062-inch K-wires may be used to perforate the surface of exposed bone through to the medullary cavity.

Blood should not be wiped away. A nonadherent dressing with antibiotic ointment should be applied as the primary layer of the bandage. Bandage changes are done at 3- to 5-day intervals. Once a complete layer of granulation tissue is present (approximately 7 to 10 days), a free skin graft is applied or ongoing wound management continued until second-intention healing is complete.

157.6.2

Drains

Drain placement is indicated during wound closure in areas with excessive dead space, areas with potential for fluid accumulation, or infected or contaminated areas (e.g., abscess, bite wound). The drain should exit from the dependent portion of the wound via a separate stab incision, not through the suture line. Ideally the drain should be covered with a bandage to prevent removal by the patient, to further compress dead space, and to keep the area clean. Drains are removed when drainage is clear or minimal (2 to 7 days).

There are two types of drains, passive and active. A Penrose drain is the best means of passive gravitational drainage. This type of drain can be secured at the proximal extent of the wound pocket with a simple interrupted suture through the skin that catches the flimsy rubber tubing while it is held in position with a hemostat. A separate opening to secure a Penrose drain proximally should never be made because this allows bacteria to migrate into the wound.

There are many types of active or closed-suction drains, which consist of a vacuum-generating reservoir connected to fenestrated tubing. These can be used only in areas that can be closed completely because a vacuum must be created within the wound. There are numerous commercially available closed-suction drains such as the J-VAC (Johnson & Johnson, Arlington, TX) and the Sil-Med Vacuum drain (Sil-Med Corp., Taunton, MA), which has a grenade-type reservoir. There are also several ways to make closed suction devices.[1,12] A butterfly catheter and red-top blood collection tube can be used for small spaces. Intravenous tubing connected to a 60-ml syringe with the plunger held open with a pin can be used to drain larger spaces.

157.7

BANDAGING

Good bandaging practice is essential to maintaining and protecting the wound. Ideally a bandage should cover all open wounds. A bandage consists of three layers: (1) primary, (2) secondary, and (3) tertiary layers. The necessary supplies are listed in Box 157-1.

The primary layer is the dressing applied directly to the wound. This layer determines the purpose of the bandage by whether it is an adherent or nonadherent dressing. The secondary layer is composed of padded material that aids in absorption of exudates. The tertiary layer is the outermost protective layer that holds the others in place.

157.7.1

Box 157-1 Materials for Dressing Changes

- Sterile lubricating jelly, sterile gauze, umbilical tape, sterile impermeable drape material, cast padding, 18-gauge needles, 35- to 60-ml syringe, Vet Wrap or Elastikon
- Triple antibiotic ointment, silver sulfadiazine

- Isotonic crystalloids such as lactated Ringer's solution or 0.9% saline
- 4-0 to 0 monofilament, absorbable and nonabsorbable suture material
- A variety of splints for forelimb and hind limb stabilization

An *adherent dressing* is used when the wound is in the debridement phase, providing mechanical debridement. The most common of these is the *wet-to-dry dressing,* in which sterile gauze sponges soaked with sterile saline are wrung out and applied directly to the surface of the wound, then covered with dry sterile gauze sponges. The dry sponges soak up moisture from the wet ones, and this wicking action causes necrotic tissue and debris to adhere to the sponges when they are removed. It is often necessary to wet the dressing slightly with sterile saline to allow easier removal and to make it less uncomfortable for the patient.

During the debridement phase, it is necessary to change the dressing and bandage at least once daily. Sometimes it will be necessary to change it up to 3 times a day initially, depending on how dirty the wound is or if moisture quickly “strikes through” to the outer layer of the bandage.

Nonadherent dressings are used when a healthy, pink granulation bed has covered the surface of the wound and it is no longer infected. Nonadherent dressings help retain moisture, promote epithelialization, and prevent wound dehydration.[1] The most commonly used nonadherent dressings are semiocclusive, meaning that they are permeable to air and maintain a moist environment while allowing exudates to be absorbed from the wound surface. Examples include cotton pads such as Telfa pads (Kendall) or wide-mesh gauze impregnated with petrolatum, such as Adaptic (Johnson & Johnson).

Once the primary layer is applied, the next layer can be either a soft padded bandage or a tie-over bandage. Soft padded bandages are used to protect soft tissue wounds on the limbs, and a splint can be incorporated between the second and third layers to stabilize distal fractures or ligamentous injuries. With these bandages, the secondary layer is rolled cotton that is held in place with rolled gauze. The splint is placed over the cotton and under the gauze. The tertiary layer is often Vet Wrap or Elastikon (placed over the secondary layer but without compression of the bandage or wound).

The *tie-over bandage* is used for wounds on areas of the body that are not amenable to soft padded bandages, such as the flank, perineum, or hip areas.[5] Materials include 2-0 to 0 nylon, umbilical tape, gauze, and water-impermeable drape material. Loose suture loops are applied circumferentially around the wound (see Color Plate 157-2). The secondary layer consists of several layers of dry gauze squares or laparotomy sponges that are applied for padding and moisture absorption. The tertiary layer is a water-impermeable drape cut to fit the wound, and then all three layers are held in place by the umbilical tape that is looped through the sutures in a shoelace fashion.

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The bandage should be protected from the patient by judicious use of an Elizabethan collar. If the bandage is on a limb, the foot should be covered with a strong plastic bag taped to the bandage when the patient is taken outside to keep it from getting wet or dirty. The bandage should be changed immediately when it gets wet, dirty, or slips, or when there is strike-through from the wound.

Table 157-1 Antibiotic Use Recommendations in Wound Management[1,15]

Antibiotic Use	Situation
Indicated	Obvious local or systemic signs of infection
	Wounds older than 6 hours
	Deep tissue injury involving muscle, fascia, bone, tendon
	Wounds likely to become infected such as bite wounds, penetrating wounds, and wounds involving body orifices
	Wounds requiring staged debridement, wet-to-dry bandaging
	Prophylactic use to prevent contamination of surrounding normal tissues
	To keep bacterial numbers low when planning a flap or graft
	Chronic nonhealing wounds
	Immunocompromised patient or one that has other condition that might jeopardize healing (e.g., diabetes or Cushing's disease)
May not be indicated	Clean wounds
	Superficial wounds less than 6 hours old
	A contaminated wound that can be converted easily to a clean wound with primary closure
	Wounds with a mature, healthy granulation bed

157.8 ANTIMICROBIAL THERAPY

The most common bacterial wound pathogens include gram-positive *Staphylococcus* spp and *Streptococcus* spp and gram-negative organisms such as *Escherichia coli, Enterococcus, Proteus* spp, and *Pseudomonas* spp.[3,4,13,14] When humans are bitten by dogs and cats, *Pasteurella multocida* is a common oral pathogen,[13] and the most common anaerobic isolates in bite wounds include *Bacillus* spp, *Clostridium* spp, and *Corynebacterium* spp.[14] Often *Pseudomonas* will be an acquired infection on the surface of the granulation bed, noticeable by the wound's slimy feel and obvious pungent odor. Rarely does this cause systemic infection and thus does not necessitate systemic antibiotic use.

Antibiotics are not an excuse for inappropriate wound care. Debridement, lavage, and bandaging are the most important parts of wound management, promoting healing of the tissues and creating an environment that negatively affects the ability of bacteria to proliferate. Systemic antibiotics are indicated for contaminated and infected wounds to help eliminate bacteria and promote healing.[15] Some clean, recent wounds, such as sharp lacerations, do not require microbial evaluation,[1] and superficial wounds that are easily debrided and closed may require only perioperative antibiotic use (Table 157-1).

If a wound appears infected on presentation, a Gram stain can be done to determine the predominant bacterial population and help in determining. the initial antibiotic selection. Culture and sensitivity testing of the wound should be done *after* initial debridement and lavage.

For superficial wounds in systemically stable animals, it is best to start with a bactericidal antibiotic that is effective against gram-positive bacteria, such as cefazolin or cephalexin pending culture and sensitivity results (see Chapter 108, Gram-Positive Infections). Infected, deeper wounds may require a broader-spectrum antibiotic such as amoxicillin with a β-lactamase inhibitor (Unasyn or Clavamox). With bite wounds, the most commonly cultured bacteria (*Staphylococcus, E. coli, Enterococcus* spp) were 100% sensitive to Clavamox.[14] A recent paper[14] suggests that initial antibiotic coverage for severe bite wounds should include intravenous ampicillin and either a fluoroquinolone or aminoglycoside. If the wound becomes infected, another culture of the wound is recommended because initial results taken during the first surgical debridement are of little value in predicting the organism involved. These antibiotic recommendations can also apply to most other types of severe wounds or trauma resulting in extensive deep tissue disruption.

When systemic antibiotics are used, they should be started as soon as possible after the injury, used for a minimum of 5 to 7 days, and changed if necessary based on culture and sensitivity results.[1] Wounds can be sampled for repeat culture after 3 to 4 days to determine the effectiveness of antibiotic therapy. If wound healing does not appear to be progressing after the first 2 to 3 days or the animal's condition is worsening, a change in antibiotic therapy may be indicated. Once mature granulation tissue has become established, antibiotic usage is usually unnecessary because this tissue is resistant to infection.[1]

Topical antibiotics are often used to decrease bacterial populations on the wound, but they should always be used in conjunction with debridement and lavage.[1] The following medications are best used by spreading a thin layer on a nonadherent pad that is the primary layer of the bandage. Triple antibiotic ointment is more effective for preventing infection than treating it, and it has poor activity against *Pseudomonas*. Silver sulfadiazine cream is fairly broad-spectrum and enhances epithelialization. It is the agent of choice for burn wounds. Nitrofurazone is a broad-spectrum antimicrobial agent with hydrophilic properties; it dilutes exudate. Gentamicin sulfate is good for wounds infected with *Pseudomonas* and is often used on open wounds before skin grafting is done.[1]

157.9 PATIENT CARE

Patients with extensive wounds that require daily debridement and bandage care may need intensive care initially (see Chapters 64 and 65, Daily Intravenous Fluid Therapy and Shock Fluids and Fluid Challenge, respectively). They also require pain management (see Chapter 164, Analgesia and Constant Rate Infusions) and nutritional therapy (see Chapters 13 and 14, Enteral Nutrition and Parenteral Nutrition, respectively) while recovering from trauma. Table 157-2 lists some of the commonly used pain medications and antibiotics with their dosages.

Table 157-2 Drugs Commonly Used During Wound Management

Key Drug	Drug Class	Dosage Range	Frequency	Route	Indications
Amoxicillin or ampicillin	Extended-spectrum penicillin antibiotic	15 to 22 mg/kg	q6-8h	PO (amoxicillin) or IV or IM (ampicillin)	Infection, dirty wounds
Amoxicillin-clavulanic acid	Extended-spectrum penicillin antibiotic with β-lactamase inhibitor	13.75 to 20 mg/kg	q8-12h	PO	Superficial wounds
Amoxicillin-sulbactam	Extended-spectrum penicillin antibiotic with β-lactamase inhibitor	13.75 to 20 mg/kg	q8-12h	IV, IM	Superficial wounds
Cefazolin	Cephalosporin antibiotic	22 mg/kg	q6-8h; for perioperative use give 20 min before surgery and then q2h until surgery is complete	IV, SC	Infection, dirty wounds
Enrofloxacin	Fluoroquinolone antibiotic	5 to 20 mg/kg (do not exceed 5 mg/kg q24h in cats)	q24h (or divided q12h)	IV	Infection, dirty wounds
Metronidazole	Antimicrobial	7 to 10 mg/kg	q8-12h	PO, IV	Anaerobic infection, dirty wounds
Hydromorphone or oxymorphone	Opioid	0.05 to 0.1 mg/kg	q4-6h	IV, IM	Pain management
Acepromazine	Phenothiazine anxiolytic	0.005 to 0.02 mg/kg	As needed	IV, IM	Used with oxymorphone for restraint with bandage changes
Fentanyl patch (Duragesic)	Opioid	<10 kg: 25 μg 10 to 20 kg: 50 μg 20 to 30 kg: 75 μg >30 kg: 100 μg	Takes 12 hr to peak effect, lasts 72 hr	Dermal	Pain management

Epidural morphine (Duramorph)	Opioid	0.1 mg/kg diluted in 0.1 ml/kg 0.9% saline, not to exceed 6 ml	Produces pain relief in 30 to 60 min that lasts 10 to 24 hr	Epidural	Pain management; local analgesia if combined with bupivacaine (use 0.1 ml/kg of 0.5% bupivacaine instead of saline)
Bupivicaine 0.5%	Local anesthetic	1.5 mg/kg maximum dose	Duration of effect 4 to 6 hr	Local block	Pain management, early assessment, aid in restraint during debridement
Vitamin A	Vitamin	10,000 IU/dog	Once a day	PO	Antagonizes the effect of corticosteroids on wound healing

IM, Intramuscular; *IV,* intravenous; *PO,* per os; *SC,* subcutaneous.

157.10 COMPLICATIONS

The biggest concern for the clinician managing severe wounds is poor wound healing. Anemia, severe trauma, or hypovolemia can delay wound healing due to poor oxygen delivery to the wound. Poor perfusion and nutritional status can also have detrimental effects on healing. Serum protein levels less than 2 g/dl impedes wound repair by decreasing fibrous tissue deposition.[6] Infection and foreign bodies cause intense inflammatory reactions that interfere with healing. Patients with cancer that are receiving chemotherapy or those who have had radiation therapy to the area of the wound will also be prone to delayed wound healing. Patients with diabetes, uremia, liver disease, or hyperadrenocorticism are susceptible to infection or delayed healing as well. Corticosteroids decrease the inflammatory phase of healing and the rate of protein synthesis; however, vitamin A can antagonizes these detrimental effects of corticosteroids.[6]

Most wounded patients are dogs; however, cats often present the more challenging cases. Axillary wounds in cats can be particularly difficult to manage. An experimental study found that cats have significant differences in wound healing compared with dogs.[16] Sutured wounds in cats were only half as strong as those in dogs by day 7, and cats demonstrated significantly less granulation tissue production than dogs did in wounds that were evaluated for second-intention healing.

Lack of bleeding or negative sensation in a limb indicates a poor prognosis and may necessitate amputation. These changes may not be predictable at the time of the initial evaluation.

As with any surgery other complications can include infection, dehiscence, and scarring. Contracture in limb wounds that are allowed to close by second intention can result in decreased mobility and may require referral to a surgeon for skin reconstruction.

157.11

PROGNOSIS

The owner should be advised as early as possible of the prognosis, extent of care involved, and cost. Prognosis depends on the extent of injury and the location. Some wounds may be irreparable, leading to the loss of a limb. Cost depends on the extent of the injury and increases with multiple injuries and if fracture repair or abdominal exploration is required. Length of hospitalization depends on the extent of debilitation, whether intravenous fluids or a feeding tube is required, and whether daily bandage changes and wound debridement are needed. Costs of $3000 or more are not uncommon if injuries require daily bandage changes and wound debridement, and expenses can go up to $6000 or more if fracture repair is needed. In some cases, patients can be treated on an outpatient basis with bandage changes every other day. Complicated wound healing can take several months and require multiple surgical procedures.

157.12

SUGGESTED FURTHER READING*

DT Crowe: Emergency care of wounds. *DVM Best Pract*. February11, 2002, *Article with excellent step-by-step instructions on managing the trauma patient with wounds. Companion articles in this periodical, a supplement to DVM* Magazine, *useful as well*.

DB Davidson: Managing bite wounds in dogs and cats. Part II. *Comp Cont Educ Pract Vet*. **20**, 1998, 974, *The second part of a two-part article that goes in depth on surgical debridement, drains, and bandaging; includes useful tables and intraoperative photos*.

TW Fossum, CS Hedlund, DA Hulse, et al.: Surgery of the integumentary system. In TW Fossum (Ed.): *Small animal surgery*. ed 2, 2002, Mosby, St Louis, *Best surgery textbook for those who want to invest in just one. Chapter on the skin good for getting started and goes into some depth on more advanced reconstructive techniques*.

KA Mathews, AG Binnington: Wound management using sugar. *Comp Cont Educ Pract Vet*. **24**, 2002, 41–50, *An article that reviews the use of sugar as an inexpensive dressing to clean and debride wounds*.

SF Swaim, RA Henderson: In *Small animal wound management*. ed 2, 1997, Williams & Wilkins, Baltimore, *An excellent text on wound management, especially for the student, intern, and resident; includes useful tables and illustrations and the best review of topical agents for wounds*.

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* See the CD-ROM for a complete list of references

158 Chapter 158 Thermal Burn Injury

Caroline K. Garzotto, VMD, DACVS

158.1 KEY POINTS

- Electric heating pads, motor vehicles with hot mufflers, and fire exposures are the most common sources of burn injuries seen in the veterinary patient.
- If the injury is from a fire exposure, the patient should be assessed for smoke inhalation (see Chapter 28, Smoke Inhalation).
- If more than 20% of the total body surface area is involved, cardiovascular shock, major metabolic derangements, and sepsis can occur. These patients will need both medical and surgical treatment.
- Burn wounds may take several days to “declare” themselves, because heat dissipates slowly from burned skin.
- The eschar should be removed early to help establish a healthy granulation bed and prevent infection.
- Silver sulfadiazine is the mainstay of topical treatment for burn wounds.
- Cost of treatment and prognosis, especially in animals with severe metabolic derangements needing critical care, should be thoroughly discussed with owners.

158.2 INTRODUCTION

Thermal burn wounds are relatively uncommon in veterinary medicine. The most common sources of burns in small animals include electric heating pads, fire exposures, scalding water, stove tops, radiators, heat lamps, automobile mufflers, improperly grounded electrocautery units, and radiation therapy.[1] Most burn wounds can be managed the same as traumatic wounds (see Chapter 157, Wound Management). Like traumatic wounds, burn wounds can be labor intensive and expensive for the owner. In addition, numerous metabolic derangements can adversely affect the patient, prolong hospitalization, and complicate the recovery.

158.3 DEFINITIONS

Burn wounds are assessed using two major parameters: the degree of the injury and the percentage of body surface area involved. First, a review of skin anatomy is helpful.[1] The most superficial layer of skin is the epidermis and the deeper layer of skin is the dermis. The dermis is comprised of a superficial plexus and a middle plexus, where hair and glandular structures arise. Below the dermis lies the hypodermis, which contains the deep or subdermal plexus and the panniculus muscle. The subdermal plexus brings the blood supply to overlying skin through the superficial and middle plexus. Capillary loops in the superficial plexus supply the epidermis; however, they are poorly developed in the dog and cat compared to humans, which is why these animals do not develop blisters.[1]

Although these are now considered older terms, many physicians still like to refer to burn wounds as *first-degree, second-degree,* and *third-degree injuries* (Table 158-1).[1,2] First-degree burn wounds are superficial and are confined to the outermost layer of the epidermis. The skin will be reddened, dry, and painful to touch.

Second-degree burn wounds are partial-thickness injuries that involve the epidermis and a variable amount of the dermis. If only the superficial part of the dermis is affected, there will be thrombosis of blood vessels and leakage of plasma. The hair follicles are spared. In deeper partial-thickness burns, hair follicles are usually destroyed, the skin appears yellow-white or brown, and there is decreased sensation except to deep pressure.[1]

Third-degree burn wounds are full-thickness injuries that have destroyed the epidermis and dermis and can affect deeper tissues such as muscle, tendon, and bone. The skin is leathery and charred and lacks sensation. When burned, skin retains heat, so an accurate assessment of the degree of the wound may not be apparent initially.[1] It can take up to 3 days for the burn to “declare” itself, and during that time thermal injury and circulatory compromise from thrombosed vessels can continue.

Patients with burns involing more than 20% of their total body surface area (TBSA) can have serious metabolic derangements. Patients with more than 50% of their TBSA involved have a poor prognosis, and euthanasia should be discussed with the owners as a humane alternative. TBSA can be estimated in animals using percentages allotted to body area using the rule of nines as described in Table 158-2.[1-3]

When skin is severely burned, it forms an eschar within 7 to 10 days. Eschar is a deep cutaneous slough of tissue composed of full-thickness degenerated skin.[4] It appears as a black, firm, thick movable crust that separates from the surrounding skin, and purulent exudates often lie beneath it (Color Plate 158-1).

158.4 PATIENT ASSESSMENT AND MEDICAL MANAGEMENT

The patient should be assessed immediately for airway, breathing, and circulatory compromise as for all trauma patients (see Chapter 2, Patient Triage). Following a full physical examination, including inspection of the patient from head to foot pads, an assessment of the degree and TBSA of the burn wounds should be performed to help determine prognosis and the extent of treatment necessary. Blood should be collected for evaluation of packed cell volume, total solid and electrolyte levels, and blood gas parameters, minimally.

Table 158-1 Burn Wound Assessment and Healing

Degree	Depth	Appearance	Healing
First	Superficial	ErythematousPainful to touch	Healing rapid, reepithelializes in 1 week with topical wound management No systemic affects
Second	Superficial partial thickness	Epidermis will be charred and sloughs; plasma leakage occurs Hair follicles spared Painful to touch	Healing by epithelialization from the wound margin with minimal scar in 10 to 21 daysMay have systemic effects
Second	Deep partial thickness	Skin appears black or yellow-whiteHair follicles destroyedDecreased pain sensation	Healing by contraction and epithelialization but scarring significant without surgical interventionSignificant systemic effects expected
Third	Full thickness	Skin is black, leathery; muscle, bone, tendons can be affectedEschar insensitive to touch	Healing often requires extensive surgical intervention, possible skin grafts and flaps May have life-threatening systemic effects

Table 158-2 Estimating Total Body Surface Area Burned

Area	Percentage (%)	Total %
Head and neck	9	9
Each forelimb	9	18
Each rear limb	18	36
Thorax	18	18
Abdomen	18	18
TOTAL	72	99

683

684

158.4.1 Metabolic Derangements

If more than 20% of a patient's TBSA is burned or if the wounds are classified as second or third degree, hypovolemic shock should be anticipated. As a result of capillary thrombosis and plasma leakage, massive amounts of fluid are retained in the wound leading to burn wound edema.[3] This results in the loss of fluid and electrolytes, with the most dramatic losses occurring during the first 12 hours. Systemic abnormalities should be anticipated, including anemia, hypernatremia or hyponatremia, hyperkalemia or hypokalemia, acidosis (metabolic and respiratory), oliguria, and prerenal azotemia. The course of the systemic abnormalities changes with time.[2]

Hemoconcentration will be noted initially because of the dramatic loss of plasma; however, red blood cell hemolysis also occurs simultaneously from both direct damage and destruction through the damaged microcirculation. The patient should be monitored for disseminated intravascular coagulation (DIC), upper airway edema and oliguria. Between days 2 and 6, the patient should be assessed for anemia, DIC, immune dysfunction, systemic inflammatory response syndrome, and early burn wound infection. From day 7 and on, the clinician should watch closely for hyperthermia, hyperventilation, pneumonia, sepsis, and wound demarcation.

Fluid losses can result in hypovolemic shock (see Chapter 65, Shock Fluids and Fluid Challenge). After initial shock resuscitation with isotonic crystalloids up to 90 ml/kg IV in dogs (50 ml/kg in cats) and synthetic colloids or blood products, if needed, total fluid delivery rate during the first 24 hours should be 1 to 4 ml/kg body weight × % TBSA burned.[2] After 12 to 24 hours, when vascular permeability is stabilized, a constant rate infusion (CRI) of synthetic colloids (e.g.,hydroxyethyl starch, dextran-70) may be beneficial at a rate of 20 to 40 ml/kg/day. Plasma is given at 0.5 ml/kg body weight × % TBSA burned in humans, although this has not been investigated in dogs and cats. By 48 hours after injury, plasma volume is mostly restored, and thus patients are at high risk for generalized edema and fluid overload from the high initial demands for fluid replacement.[3] Ideally, fluid therapy should be adjusted for the individual patient based on cardiovascular stability, central venous pressure (0 to 10 cm H_2O), and urine output (>1 ml/kg/hr).

158.4.2 Nutrition

The importance of adequate nutrition cannot be overemphasized in assisting with healing of burn wounds, because of the fragile metabolic state of the patient. Nutritional requirements should be based on the patient's needs; an initial estimate is made by calculating the resting energy requirement. The diet should be high calorie, high protein and the quantity of food can be increased as tolerated by the patient.

It is best if the patient can eat voluntarily, but if the animal is not consuming adequate nutrition, an esophagostomy tube should be placed or total parenteral nutrition commenced (see Chapters 13 and 14, Enteral Nutrition and Parenteral Nutrition, respectively). Gastrointestinal (GI) protectants (famotidine at 0.5 to 1 mg/kg PO or IV q12-24h) are recommended to compensate for GI hypoperfusion and ulceration secondary to hypovolemic shock (see Chapter 181, Gastrointestinal Protectants).

158.4.3 Patient Comfort

Although severely damaged skin is often numb, deeper viable tissues and surrounding areas are often hypersensitive and thermal damage may be ongoing; thus one should assume that burn patients experience extreme pain. Good systemic analgesics include oxymorphone and hydromorphone (0.05 to 0.1 mg/kg IV q4-6h) and fentanyl as a CRI (2 to 5 μg/kg/hr IV). A fentanyl patch may not be appropriate in animals with more than 20% TBSA burned or who are still being treated for hypovolemic shock. Good nursing care is important, and animals should be turned every 4 hours if recumbent to prevent decubitus ulcers. Passive range-of-motion limb exercises can help prevent edema and maintain mobility.[2]

158.4.4 Antibiotics

Sepsis is one of the greatest threats to burn patients with extensive TBSA involvement, because bacteria can colonize and proliferate in wounds that have lost the protective skin barrier. The best way to prevent local and systemic infection is to protect the wound from contamination in the hospital environment, and to remove all necrotic tissue and purulent exudates from the wound surface as aggressively as possible through serial debridement. Systemic antibiotics are not indicated unless the patient is immunocompromised, has pneumonia or pulmonary injury, or sepsis is suspected. Topical antibiotics are the antimicrobial treatment of choice (see Burn Wound Management in the following section). Because most invasive burn wound infections are caused by

Pseudomonas or other gram-negative organisms, antibiotics against these bacteria are administered empirically until culture and sensitivity results are available (see Chapter 109, Gram-Negative Infections).[3]

158.5 BURN WOUND MANAGEMENT

Although early wound closure is the primary goal to decrease further electrolyte, protein, and fluid losses, this is not expected to take place for at least 3 to 7 days while the wound is “declaring” itself. Daily wound care, however, is critical. Once systemically stable, the patient is sedated with neuroleptanalgesia or placed under general anesthesia and the fur is liberally clipped to assess the damage. If fur pulls easily out of the skin, the wound is likely a deep partial-thickness or full-thickness burn (see Table 158-1).

If the patient presents within 2 hours of the burn injury (which is usually not the case), cold water lavage for 30 minutes will often help to release heat from the skin and limit the depth of injury.[1] The temperature of the water should not be below 3° C, and if large body surface areas require treatment, it is important to prevent iatrogenic hypothermia. The affected area can be submerged in a cold water bath if it is on a limb, and cool towels or cool water from a spray nozzle can be applied to other areas.

Treatment of the wound then depends on its depth. In superficial burns or superficial partial-thickness burns, it may be appropriate to use daily lavage and topical agents alone until the depth of the wound is determined if the wound goes deeper.[1] Deep partial-thickness and full-thickness burns require debridement. Debridement can be done in three ways: conservatively, enzymatically, or aggressively with surgery.[1] Conservative debridement is often used for the first 3 to 7 days, until more aggressive surgical debridement can be performed based on the status of the wound and of the patient.

Daily treatment of burn wounds with conservative debridement involves hydrotherapy, removal of necrotic tissue, topical therapy, and bandaging. This may need to be done more than once a day initially for wounds that are particularly necrotic or exudative. Hydrotherapy consists of gentle lavage of the wound with room temperature sterile saline or lactated Ringer's solution. This helps to loosen and separate any nonviable or necrotic tissue from the surface of the burn. The irrigants should be delivered using a 35-ml syringe and a 19-gauge needle to create a pressure of 8 psi. Higher pressures may induce tissue trauma and cause deeper seeding of bacteria into the burn. A wet-to-wet dressing under a bandage can also be placed on burns for several hours at a time to slowly loosen the necrotic tissue and facilitate debridement.[1,4]

Conservative debridement is characterized by the daily serial piecemeal removal of necrotic tissue (black and hard, burned skin) using aseptic technique, with either sterile gauze or sterile scissors and thumb forceps. Because necrotic tissue is without sensation, this may not require daily anesthesia; however, manipulation of deeper viable tissues and surrounding hyperemic areas will likely be painful during lavage. This form of debridement is acceptable initially when there is no clear definition of nonviable tissue or when it is necessary to be conservative in areas overlying tendons, ligaments, and bone.[1]

Enzymatic debridement is the use of topical agents to soften, loosen, and digest necrotic tissue, making removal possible with gentle lavage. The advantage is that it does not require general anesthesia and involves sparing of healthy tissue. Because some of the commercially available agents are expensive, it is most cost effective to use them on small limb wounds. The most common of these enzymatic topical agents is trypsin-balsam of Peru castor oil (Granulex, Pfizer Animal Health, West Chester, PA). It is recommended that this be applied only in the early stages of wound therapy and that its use discontinued once a healthy bed of granulation tissue has been established.[4]

Aggressive surgical excision of an entire burn wound requires general anesthesia and is indicated in deep partial-thickness and full-thickness burn wounds that may otherwise take days or weeks to be debrided conservatively. This is done most easily on large areas of the trunk or small areas of the limbs, which can then be closed primarily (Color Plates 158-2 and 158-3). If the area cannot be closed primarily, it will take about 5 to 7 days for a healthy granulation bed to form and then a flap or skin graft surgery can be performed.[1]

158.5.1 Topical Agents

Following hydrotherapy and debridement, topical agents and bandages are applied. Aloe vera cream has antithromboxane effects that prevent vasoconstriction and thromboembolic seeding of the microcirculation.[4] Early use can help prevent progression of superficial partial-thickness burns. Aloe vera is applied liberally to the surface of the wound with a sterile gloved finger within the first several days of injury while the patient is sedated, because these wounds are painful when touched. The wound can be covered with a nonadherent dressing and a bandage. The bandage is changed at least once a day.

Silver sulfadiazine is the most well-known burn cream used in humans and animals. It has a wide spectrum of bactericidal activity against gram-positive and gram-negative bacteria and *Candida*. The cream is placed directly on the wound under the contact layer of a bandage using sterile gloves. For very large areas that are not amenable to bandaging, patients can be treated “open” without a bandage, by slathering silver sulfadiazine over the wound and keeping the patient confined in a low-fomite environment (empty clean cage with no blankets or stuffed toys).[1,4] The cream can be rinsed off gently before reapplication up to 2 to 3 times a day, if needed. Silvadene can be used during both the early debridement stage under wet-to-wet dressings and through the repair stages of healing using nonadherent bandages.

Unpasteurized honey has been shown to demonstrate many favorable properties in the management of wounds, including burn wounds (see Chapter 157, Wound Management). It has been shown to outperform more expensive commercial products.[5] Healing properties of honey are varied; honey decreases inflammatory edema, accelerates sloughing of necrotic tissue, and provides a rich cellular energy source, promoting a healthy granulation bed. In addition, honey has antibacterial properties due to its high osmolarity, acidity, and hydrogen peroxide content. The hydrogen peroxide is present in levels that are harmless to healthy tissue. Honey can be used during the debridement phase and also over infected granulation tissue.

Honey is applied to the wound after hydrotherapy and debridement of necrotic tissue. Gauze sponges soaked in honey are applied directly to the wound as the primary layer and then covered with an absorbent second layer to prevent it from leaking out of the bandage.

158.5.2 Closure Options and Healing

Superficial and partial-thickness burn wounds have a favorable outcome with no surgical intervention. These wounds reepithelialize quickly and can heal within 1 to 3 weeks with open wound management. If only the superficial layer of the dermis is involved in partial-thickness burns, healing can be rapid. The overlying burned epidermis will slough, and healthy epithelium will be apparent below. Deeper burns involving the hair follicles, especially if they are large, can heal more slowly (up to 3 weeks). Deep dermal partial-thickness and full-thickness burns heal by contraction and epithelialization once a healthy granulation bed has been created by diligent debridement. These wounds can eventually closed primarily. Full-thickness burns covering large areas of the body or on the limbs may require skin grafts or skin flaps for complete closure.

Hyperbaric oxygen therapy has not been well studied in dogs and cats but may promote angiogenesis (which is fostered by the increased oxygen gradient), collagen deposition, reepithelialization, cellular respiration, and oxidative killing of bacteria. In addition, decreased edema following hyperbaric therapy allows better diffusion of oxygen and nutrients through the affected tissues, while relieving pressure on surrounding vessels and structures. There is limited access to hyperbaric oxygen chambers for dogs and cats, but this may prove to be a beneficial treatment strategy in the future.[6]

Vacuum-assisted closure strategies have been used with success in humans with burn injuries, especially following graft placement, to promote the removal of interstitial edema, increase local blood flow, and stimulate granulation tissue formation. Tissue bacterial counts are also decreased with this technique; however, veterinary research is lacking.[7]

158.5.3 Complications

Scarring and wound contracture are the biggest complications in patients with burn wounds left to heal by second intention. This is particularly a concern for burn wounds in the axillary or inguinal areas or around joints, which can lead to decreased mobility and range of motion of the limbs. Wounds in these areas should be managed by someone experienced in reconstructive surgery, because these cases most likely will require skin grafts or flaps.

158.6 SUGGESTED FURTHER READING*

N Dhupa, MM Pavletic: Burns. In R Morgan (Ed.): *Handbook of small animal practice*. ed 4, 2003, Saunders, *An easy-to-follow veterinary text in outline format.*

KA Mathews, AG Binnington: Wound management using honey. *Comp Cont Educ Pract Vet*. **24**, 2002, 53, *An interesting article with historical perspective and review of research on the use of honey in medicine. Includes nice photos showing examples of treatment burn wounds with honey*.

ER Pope: Burns: Thermal, electrical, and chemical burns and cold injuries. In D Slatter (Ed.): *Textbook of small animal surgery*. ed 3, 2003, Saunders, Philadelphia, *A chapter from the well-known veterinary surgery textbook with a very thorough review of burn pathophysiology*.

SF Swaim, RA Henderson: In *Small animal wound management*. ed 2, 1997, Williams & Wilkins, Baltimore, *An excellent text especially for the student, intern, and resident. Has nice tables and illustrations*.

* See the CD-ROM for a complete list of references

159 Chapter 159 Electrical and Lightning Injuries

F.A. Mann, DVM, MS, DACVS, DACVECC

159.1 KEY POINTS

- Electrical injury results from the direct effects of the electrical current and from the transformation of electrical energy to heat.
- The severity of electrical injury depends on the resistance of the stricken body part, the nature of the current, and the intensity of the current.
- The most common electrical injury in small animals occurs when young dogs and cats chew on household electrical cords.
- Clinical manifestations of electrical injury include surface burns, cardiac arrhythmias, respiratory distress, and neurologic abnormalities, and treatment is tailored to the clinical effects that are evident.
- Dogs and cats are less likely to be struck by lightning than are large animal species but, when struck, dogs might be more susceptible to the effects of lightning than are humans.

159.2 INTRODUCTION

Electrocution may occur by contact with high-voltage or low-voltage electrical sources or by a lightning strike. It is generally accepted that chewing through household electrical cords is the most common cause of electrocution in dogs and cats. From 1968 to 2003, a database from several institutions* recorded that 280 dogs and 92 cats sustained electrical injuries. Of these, 54 dogs and 26 cats had chewed electrical cords, and 4 dogs and no cats were identified as having been struck by lightning. It is likely that many of the unspecified electrocutions were low-voltage injuries from chewing household electrical cords.

* The Veterinary Medical Data Base (VMDB), Purdue University, West Lafayette, IN (http://www.vmdb.org). The VMDB does not make any implicit or implied opinion on the subject of this chapter.

159.3 MECHANISM OF ELECTRICAL INJURY

The mechanisms of electrical injury are related to the direct effects of the electrical current and the transformation of electrical energy to heat. The electrical current may disrupt electrophysiologic activity, leading to muscle spasms, cardiac arrhythmias, loss of consciousness, and respiratory arrest.[1-3] Direct cellular injury may occur through the process of electroporation. Electroporation is the development of momentary holes in cellular membranes induced by electrical shock. The holes allow passage of macromolecules across membranes, causing osmotic damage to cells.[4]

As electrical current is transformed to heat, intracellular and extracellular fluids may become superheated, resulting in coagulation of tissue proteins, thrombosis of small vessels, and degenerative changes in small arterial walls.[1,2,4] Ultimately, the result is necrosis of the superheated tissues and those tissues that become ischemic from the vascular consequences. Direct thermal injury may also occur from arcing of a current that leaves the electrical source, crosses an air gap, and strikes tissue.[1]

The severity of electrical injury varies depending on the electrical resistance of the part of the body that is struck, the nature of the current (alternating versus direct), and the intensity of the current (amperage).[1,4] Less energy will be transferred to areas of the body that have high resistance to electrical flow. Dry skin has high resistance; therefore less energy will be transferred in dry skin than in wet skin. Wet skin and moist mucous membranes have low electrical resistance; therefore one can expect high flow of electricity in these tissues and propensity for maximal tissue damage.

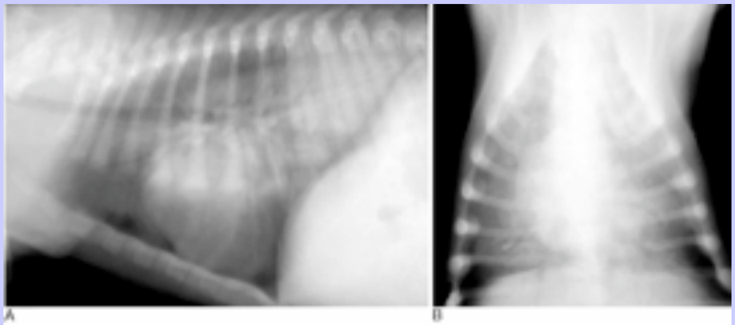
Alternating currents tend to cause more severe injury than direct currents at the same amperage. Higher exposure may occur with alternating current electricity than with direct current because the former elicits muscular contraction that prevents the victim from releasing the power source. As such, the exposure time is typically longer with alternating current than with direct current. Direct current electricity does not usually cause muscular tetany.

Given the same resistance, high-voltage electricity can be expected to cause more damage than low-voltage electricity. One might expect more injury from 240-volt outlets used for large household appliances than with 120-volt standard wall outlets. However, current (amperage) is a function of voltage divided by the resistance; therefore the magnitude of the current will depend on the affected tissue as discussed previously.[1,4]

159.4 PREDISPOSITION TO ELECTRICAL INJURY

Young dogs and cats are the most common victims of electrical injury because they are more likely to chew on electrical cords than are older animals. The average age of dogs with electrical injury has been reported to be 3.5 months (range, 5 weeks to 1.5 years; n = 29); the range of age for seven cats was reported to be 2 months to 2 years.[1] From 1968 to 2003, a database collected in several institutions* revealed that the most common age range for electrical injuries was 2 to 12 months; 186 of 280 (66%) dogs and 44 of 92 (48%) cats with electrical injuries and 38 of 54 (70%) dogs and 12 of 26 (46%) cats that sustained electrical injury from chewing electric cords were 2 to 12 months old. Seasonal predisposition is generally accepted, but there is some difference in opinion as to what time of year most injuries are seen. Holiday seasons characterized by use of decorative lights (Halloween, Christmas) certainly pose electrical risks,[4] but one study reported that 79% of canine cases occurred during the 6 months from March through August.[1]

Figure 159-1 Lateral **(A)** and ventrodorsal **(B)** thoracic radiographs of a puppy that was electrocuted by chewing an electrical cord. Note the prominent infiltration of the caudodorsal lung fields. (Courtesy Dr. Everett Aronson.)



159.5 CLINICAL FINDINGS

Surface burns may be noted at the point of contact with the electrical source. The thermal injury may be superficial, characterized by mild hyperemia, or may manifest as a severe full-thickness burn. Burns from chewing electrical cords have been noted on the lips, gums, tongue (Color Plate 159-1), and palate.[1-6] Some oral cavity electrocutions produce enough trauma to cause dental fractures and oronasal fistulas.[6]

Cardiac arrhythmias may be present, the severity of which depends on the intensity of the electrical current. Sudden death from electrical shock is likely due to ventricular fibrillation caused by low-voltage current, as with most household exposures.[4,5,7] High-voltage exposure may cause asystole.[4] Animals that survive the initial shock may experience ventricular arrhythmias. Ventricular or sinus tachycardia may be noted on presentation.

Respiratory distress is a common clinical feature noted in the form of tachypnea, cyanosis, orthopnea, coughing, or apnea. Respiratory arrest from tetanic contractions of respiratory muscles occurs during contact with the electrical source, but breathing typically resumes when the victim is separated from the source of electricity.[8]

Causes of respiratory distress include facial or nasopharyngeal edema, diaphragmatic tetany, and neurogenic pulmonary edema. Neurogenic pulmonary edema is a form of noncardiogenic pulmonary edema in which central nervous system (CNS) insult results in massive sympathetic outflow that causes pronounced vasoconstriction and systemic hypertension. As a consequence, there is marked elevation of left ventricular afterload and decreased left ventricular stroke volume, which causes blood to accumulate in the pulmonary circulation, resulting in increased pulmonary capillary pressure and subsequent edema.[9] The typical radiographic pattern is alveolar infiltration of the caudodorsal quadrant (Figure 159-1).

Respiratory distress is less severe with electrical cord-induced pulmonary edema than with other causes of noncardiogenic pulmonary edema. Likewise, there is less radiographic involvement than with other causes of noncardiogenic pulmonary edema,[9] and there is often radiographic evidence of resolving pulmonary infiltrates within 18 to 24 hours (Figures 159-1 and 159-2).[1]

Neurologic injury as a result of direct CNS stimulation may be noted immediately upon electrical contact. Stiffening of the animal has been noted by people who have witnessed a dog or cat biting an electrical cord.[3] The victim usually loses consciousness.[3] There may be focal muscle tremors or seizures, sometimes accompanied by defecation or vomiting.[3,4] Extensor rigidity and death may occur rather rapidly. Tetanic limb contraction has been noted after surviving high-voltage electrical shock.[10] The neurologic manifestations are thought to be due to electrically induced neural activity rather than electroporation and resultant tissue hypoxia, although hypoxia from excess energy consumption could play a role.[11]

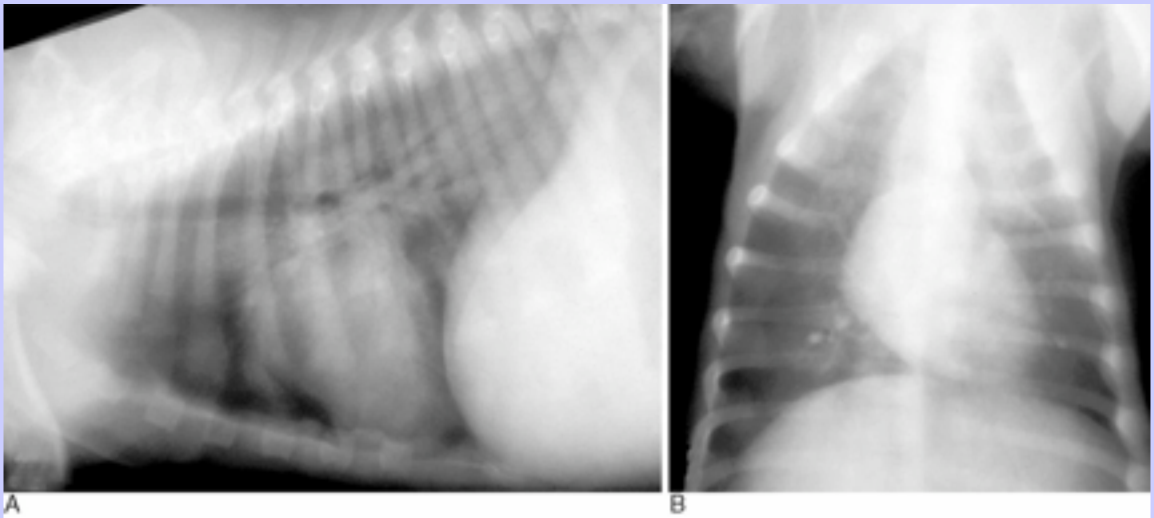
Gastrointestinal (GI) abnormalities may result from electrical interference with motility. Abdominal radiographs or ultrasonography may show GI gas patterns characteristic of ileus.[4]

Ocular manifestations of electrical injury (cataracts) are usually later findings noted several months after the episode. Cataracts are commonly seen in humans. following nearly fatal electrical injury and lightning strike and have been reported in a dog that was electrocuted by chewing an electrical cord.[12]

159.6 SECONDARY EFFECTS OF ELECTRICAL INJURY

Although complete blood count and serum chemistry results are usually within normal limits, tissue hypoxia from electrically induced ischemia and pulmonary edema may lead to necrosis of the affected tissues and subsequent hematologic changes and additional organ damage. Tissue necrosis may lead to hyperkalemia, myoglobinemia and myoglobinuria, and hemoglobinemia and hemoglobinuria.[4] Hyperkalemia may also result from excessive muscular activity during electrical shock; this muscular activity also contributes to acidemia and hyperlactatemia.[13] Hypoproteinemia may ensue in patients with severe burns.[4]

Figure 159-2 Lateral **(A)** and ventrodorsal **(B)** thoracic radiographs of the puppy in Figure 159-1 taken approximately 24 hours after the radiographs in Figure 159-1. Note the significant progress in resolution of the pulmonary infiltration. (Courtesy Dr. Everett Aronson.)



159.7 TREATMENT OF ELECTRICAL INJURY

Initial treatment at the scene of the exposure includes precautions to prevent inadvertent injury to rescuers. The source of electricity should be turned off before touching the victim. Preferably, the electricity should be turned off at the electrical panel but, alternatively, the offending electrical cord may be unplugged carefully from the outlet. Once the victim is removed from the electrical source, immediate medical attention should be sought regardless of the victim's apparent condition. Victims in cardiopulmonary arrest require cardiopulmonary-cerebral resuscitation. Better results might be expected in a hospital environment, but lifesaving techniques on the scene may be required if there is any hope of success.

Treatment for animals that survive the initial electrical insult is tailored to the clinical effects. Animals in shock are treated with intravenous fluids to expand intravascular volume because the mechanism of shock is likely a relative hypovolemia. However, because a cardiogenic component to the shock from arrhythmia and subsequently decreased stroke volume is possible, and because neurogenic pulmonary edema may develop quickly, the volume of fluids administered should be strictly controlled. Fluids that typically are given in low volumes (i.e., hypertonic saline, synthetic colloids) are recommended.

Respiratory distress requires prompt attention. Airway obstruction from edematous oropharyngeal tissues may require temporary tracheostomy tube placement. Partial obstructions may be managed conservatively with sedation and, if not contraindicated, antiinflammatory drugs and diuretics. Supplemental oxygen is recommended, but if the respiratory distress is due entirely to obstruction, relief of the obstruction should return oxygenation to normal.

Oxygen supplementation should continue until it is ascertained that neurogenic pulmonary edema has not developed or has resolved. Treatment of pulmonary edema is facilitated by furosemide, particularly if the animal received shock doses of fluids; however, caution should be exercised to prevent creating a state of hypovolemia from excessive diuresis. Bronchodilators may also be useful (see Chapter 21, Pulmonary Edema). Positive-pressure ventilation may be required if the patient is hypoxic and does not respond to supplemental oxygen (see Chapter 213, Basic Mechanical Ventilation).

Burned tissues are treated conservatively using standard wound treatment principles. Reconstructive surgery, if indicated, is performed after recovery from the electrical shock when it is determined that the tissues are healthy enough that one can expect good surgical results. Ventricular arrhythmias are managed with antiarrhythmic agents and by reversing the underlying pathophysiologic derangements (see Chapters 47 and 190, Ventricular Tachyarrhythmias and Antiarrhythmic Agents). Seizures are controlled with anticonvulsant therapy (see Chapters 98 and 186, Seizures and Status Epilepticus and Anticonvulsants). GI is best managed with early nutritional support, via an appropriate feeding tube if necessary (see Chapter 13, Enteral Nutrition).

Pain management is necessary because burn wounds are painful and because there is likely muscle soreness from excessive activity during the electrical stimulation. Initially opioids are preferred, but nonsteroidal antiinflammatory drugs may be used when GI integrity is presumed to be normal.

159.8 PROGNOSIS

The prognosis for victims that survive the initial shock episode is generally good, as long as the clinical effects are reversible. Respiratory abnormalities are the clinical effects most likely to alter prognosis. Most cases of electrically induced noncardiogenic pulmonary edema resolve quickly, but one study reported a fatality rate of 38.5%.[1] 689 690 Some animals will require follow-up surgery to treat residual effects of burns. Recovering victims should be monitored for potential long-term effects. Owners should be instructed to observe for cataract development that could occur several months after recovery.

159.9 LIGHTNING INJURY

Lightning injury is more likely to occur in large animal species[14-16] than dogs and cats because of greater outdoor exposure. However, companion animals, especially dogs, share outdoor activities with humans and, therefore, may occasionally be exposed. A carefully studied lightning strike at a scene where 2 adults and 26 girls were camping included 7 dogs.[17] Fatal injuries occurred in 4 of the girls and 4 of the dogs.

Of the surviving dogs, the smallest one, a Maltese-Poodle, escaped injury. One surviving dog sustained burns and the other suffered damage to an eye that subsequently became opaque. Because the deceased dogs were farther from the stricken tent pole than surviving humans, it was speculated that dogs might be more susceptible to the effects of lightning injury than are humans.[17] It is possible that small dogs, as in the camping scene incident, are less susceptible to lightning injury than larger dogs.[17] In cattle, adults are more likely to be struck by lightning than are calves.[15]

The pathophysiology of lightning injury is similar to that of other electrical injuries, except for the mechanism by which the electricity reaches the victim and the potential for injury from mechanical energy. There are five possible mechanisms by which lightning can deliver electrical injury to a victim: (1) direct lightning strike, (2) direct strike of an object that the victim is touching, (3) side flash from a stricken object, (4) step voltages produced by current flowing through the soil beneath, and (5) an upward streamer that does not connect or complete a full lightning strike. With the latter mechanism, injury is caused by the upward streamer of charge that is induced from an object on the ground, as a lightning leader of flash approaches the ground from a thundercloud.[17,18]

In addition to direct electrical and thermal injury, mechanical energy can be imparted to the lightning victim. A blast effect from rapid air movement caused when superheated air is then cooled may result in physical injury. Humans are often thrown to the ground and report muscle pain. Lumbosacral fracture with resultant spinal cord injury was the only lesion identified in three pigs in an outdoor pen that was struck by lightning.[16] Although not reported in dogs and cats, similar effects of mechanical energy should not be surprising.

159.10 SUGGESTED FURTHER READING*

SL Marks: Electrocution. *Proc North Am Vet Conf.* **18**, 2004, 176, *Proceedings notes that provide a concise summary of electrical cord and lightning injury in dogs and cats.*

RV Morgan: Environmental injuries. In J Hoskins (Ed.): *Veterinary pediatrics: dogs and cats from birth to six months of age*. ed 3, 2001, Saunders, Philadelphia, *First section of chapter discusses electrical shock in dogs and cats; a good overview of the causes, pathophysiology, clinical findings, treatment, and owner education.*

RH Presley, DK Macintire: Electrocution and electrical cord injury. *Stand Care Emerg Crit Care Med.* **7**, 2005, 7, *An excellent overview of electrical cord injury in dogs and cats, with a good summary of pathophysiology followed by clinical features and treatment in a quick, easy-to-read outline format.*

* See the CD-ROM for a complete list of references

160 Chapter 160 Massive Transfusion

L. Ari Jutkowitz, VMD, DACVECC

160.1 KEY POINTS

- Massive transfusion is traditionally defined as the transfusion of 1 or more blood volumes within a 24-hour period.
- Electrolyte abnormalities such as hypocalcemia, hypomagnesemia, and hyperkalemia are common following massive transfusion.
- Hemostatic defects frequently develop as a result of dilution and consumption of platelets and clotting factors.
- Hypothermia and acidosis may exacerbate hemostatic defects and are associated with a poor outcome.

160.2 INTRODUCTION

Patients sustaining exsanguinating injuries as a result of trauma, coagulopathy, neoplasia, or surgery often require massive volume replacement during the resuscitation and perioperative periods. *Massive transfusion,* the term coined for this clinical entity, has traditionally been defined as the transfusion of a volume of whole blood or blood components that is greater than the patient's estimated blood volume (90 ml/kg in the dog and 66 ml/kg in the cat) within a 24-hour period. Other definitions for massive transfusion have included the replacement of half the estimated blood volume in 3 hours or the administration of 1.5 ml/kg/min of blood products over a period of 20 minutes, reflecting an increased risk of adverse effects with rapid administration rates.[1,2] As advancements have been made in the field of human transfusion medicine, the criteria for defining massive transfusion have evolved in some studies to include transfusions of more than 20 to 50 units of blood products.[3-5]

Massive transfusion imposes an incredible drain on blood banking resources. In veterinary clinics where blood products frequently are stored in limited quantities, a massively transfused patient may deplete most or all of the hospital's blood supply, making this commodity unavailable to other patients in need. This type of expenditure is also associated with significant cost to pet owners.

Given the severity of injuries that cause near exsanguination, it should not be surprising that massive transfusion has been associated with a high mortality rate, and this has led some to question whether massive transfusion may be futile or wasteful. However, reports in the human literature have identified survival rates of between 25% to 60% following massive transfusion, and in one study of massively transfused dogs, 4 of 15 (27%) survived to discharge.[4-8] Complications following massive transfusions are numerous, however, and may include electrolyte disturbances, coagulation defects, hypothermia, alterations in acid-base status, immunosuppression, acute lung injury, other immunologic transfusion reactions, and transmission of infectious diseases.

160.3 ELECTROLYTE DISTURBANCES

Stored blood undergoes changes in both the concentration and availability of various electrolytes. Recipients of massive transfusions may therefore develop electrolyte disturbances, with hypocalcemia, hypomagnesemia, and hyperkalemia most commonly reported.[6,9] Hypocalcemia and hypomagnesemia result from the citrate that is added to blood products as an anticoagulant. Once in the body, citrate binds rapidly to both calcium and magnesium with equal affinity, resulting in decreases in ionized calcium and magnesium levels. In one veterinary study, ionized hypocalcemia was documented in 100% of cases following massive transfusion, with severe hypocalcemia (<0.7 mmol/L) noted in 20%.[8] Changes in ionized magnesium concentration in this study tended to parallel those of ionized calcium. Ionized hypocalcemia has been reported to resolve quickly once perfusion is restored, because citrate is metabolized rapidly by the liver.[10] Treatment with calcium gluconate is indicated in cases of severe hypocalcemia or when clinical signs such as hypotension, muscle tremors, arrhythmias, or prolonged QT interval manifest.

Potassium levels in stored (human) blood rise over time because of inactivation of the sodium-potassium ATPase pump by the cold storage temperatures. Humans receiving large volumes of stored blood products may therefore develop hyperkalemia. Most dogs, with the exception of Akitas and Shiba Inus, lack significant intracellular quantities of potassium in their red blood cells and, as a result, increased potassium levels are not observed in stored canine blood.[11,12] Although this would suggest that hyperkalemia in massively transfused canine patients should theoretically be less of a concern, hyperkalemia was identified in 20% of dogs in one study, a prevalence similar to that reported in human patients.[8] Hyperkalemia in these cases may have resulted from other factors related to their underlying injuries or illnesses, including potassium leakage into the bloodstream from damaged tissues, extracellular potassium shift secondary to acidosis, and reduced potassium excretion associated with oliguria.

160.4 HEMOSTATIC DEFECTS

Hemostatic defects are commonly seen in the massively transfused patient, with thrombocytopenia, hypofibrinogenemia, and dilutional coagulopathy most frequently reported. Thrombocytopenia following massive transfusion is believed to result primarily from blood loss and dilution. Blood products become devoid of platelets after 2 days of storage because the cold storage temperatures cause cell oxidation and death. Administering large volumes of these platelet-free blood products, especially after aggressive fluid resuscitation, can result in a dilutional thrombocytopenia. Thrombocytopenia resulting from dilution is generally less severe than the level that would have been predicted by the degree of dilution (i.e., the loss and replacement of 50% of a patients blood volume does not result in a 50% decrease in platelet count), because platelets are released from stores in the lungs and spleen.[13]

In studies of human patients wounded in war, nonhemostatic platelet counts of less than 50,000 cells/µl were noted only after transfusion of more than 2 blood volumes.[14] Similarly, in 15 massively transfused dogs, moderate thrombocytopenia developed in all dogs for which posttransfusion platelet counts were available, but none developed platelet counts below 50,000 cells/µl.[8]

Dilution alone, however, does not account for all of the clinical observations regarding platelet counts. Blunt trauma, shock, sepsis, or systemic inflammation associated with the underlying injuries may also result in disseminated intravascular coagulation, leading to consumption of platelets and clotting factors. Platelet dysfunction resulting from acidosis or hypothermia is another well-documented phenomenon following massive transfusion and may be as important as platelet numbers in determining likelihood of bleeding.[15]

When large quantities of intravenous fluids and packed red blood cells are administered to replace massive blood loss, the dilutional effects may result in prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT). Clotting factor consumption secondary to tissue injury may further exacerbate dilutional coagulopathy. Hemostasis is generally maintained as long as clotting factors are at least 30% of normal, and PT and aPTT values are not prolonged above 1.5 times normal.[16] Exchange transfusion models predict that loss and replacement of 1 blood volume removes slightly less than 70% of circulating factors in the plasma, so theoretically transfusions of up to 1 blood volume should not be associated with abnormal bleeding tendencies.[16] In human patients with war wounds, coagulopathy developed only after transfusion of more than 2 blood volumes.[14] Coagulopathy was identified in 70% of dogs following massive transfusion, although a correlation with transfused volumes could not be made because of the retrospective nature of the study.[8]

Human trauma centers have traditionally employed empiric formulas for plasma and platelet replacement (e.g., giving 10 units of platelet concentrates and 5 units of plasma per 10 units of packed red blood cells administered) in an effort to prevent dilutional coagulopathy. However, formula replacement has not been shown to prevent coagulopathy or to reduce transfusion requirements. Instead, serial monitoring of coagulation parameters has been recommended, with blood components administered as needed to maintain the PT and aPTT under 1.5 times normal and the platelet count greater than 50,000 cells/μl.[7,17]

160.5 HYPOTHERMIA

Hypothermia is a frequent complication of massive transfusion in human patients and was observed in 69% of dogs.[8] Hypothermia results from shock secondary to the underlying illness or injury and the subsequent administration of large volumes of refrigerated blood products. Hypothermia can have profound effects on the coagulation system. Several studies have demonstrated a strong association between severity of hypothermia and the likelihood of developing microvascular bleeding, defined as uncontrolled bleeding from catheter sites, endotracheal tubes, mucosa, and surgical incisions.[7,18,19] Although hypothermia has little effect on clotting factor levels, it has been shown to inactivate the enzymes that initiate the intrinsic and extrinsic coagulation cascades and to enhance fibrinolysis.[2,18,19] Severe hypothermia can also result in decreased platelet activity.[15,19] Unfortunately, the contribution of hypothermia to coagulopathy is often overlooked in clinical patients, because coagulation testing typically is performed at 37° C in the laboratory rather than at the patient's body temperature.[18]

160.6 METABOLIC ACIDOSIS

Another complication reported in the massively transfused patient is severe metabolic acidosis.[5,6,20] When blood is stored, glucose metabolism leads to an increase in lactic and pyruvic acids. Thus the pH of stored blood may be as low as 6.4 to 6.6.[6] When a patient is transfused with 1 or more blood volumes, severe acidosis can result. This is often compounded by lactic acidosis secondary to shock. The “bloody vicious cycle” of progressive hypothermia, persistent acidosis, and inability to establish hemostasis has been recognized increasingly in human medicine as a leading cause of death following blunt trauma.[20] The use of rapid infusers capable of quickly administering warmed blood and fluids, the increased use of warm air blankets, and the staging of laparotomy procedures to avoid prolonged hypotension secondary to anesthesia are measures that can significantly reduce the impact of hypothermia and acidosis on the coagulation system.[4,20]

160.7 IMMUNOSUPPRESSION AND WOUND HEALING

Immunosuppression has been well documented in human medicine following transfusion of large blood volumes. In one study of massively transfused human patients, the incidence of wound complications in the patients who survived for at least 1 week was 29.5%, 6 times the hospital average.[6] Similar findings of increased infection rates following transfusion have been documented in patients undergoing surgery for trauma, burns, fracture repair, gastrointestinal cancer, cardiac bypass, spinal surgery, and hip replacement.[21-29]

The mechanism by which blood transfusions reduce immune responsiveness is unclear, but donor white blood cells within the transfused blood have been implicated. These leukocytes are believed to exert immunosuppressive effects through alloimmunization, induction of tolerance in recipient lymphocytes, and release of humoral factors that suppress immune cell function. Experimental studies have identified decreased phagocytic cell function, decreased natural killer cell activity, decreased macrophage antigen presentation, and suppression of erythroid, myeloid, and lymphoid hematopoiesis as some of the changes seen following blood transfusion.[30] Leukoreduction, the use of special filters to remove white blood cells before storage, has been shown in clinical studies to attenuate some of these changes.[24]

160.8 ACUTE LUNG INJURY

Massive transfusions have also been associated with transfusion-related acute lung injury. Blood stored under standard blood bank conditions develops microaggregates of platelets, white blood cells, and fibrin that may be removed only partially when transfused through a commercial (170-micron) blood filter. Embolization to the alveolar capillary beds has been shown experimentally to occur in dogs[31] and may lead to acute lung injury. In human medicine, antileukocyte antibodies in the donor blood have been implicated as the primary cause of in vivo agglutination and subsequent embolization of recipient neutrophils to the pulmonary vasculature, although this mechanism has not yet been identified in dogs.[32]

160.9 OTHER IMMUNOLOGIC TRANSFUSION REACTIONS

Because large volumes of blood are administered from a variety of donors, and because there is frequently insufficient time for typing or cross-matching, massively transfused patients may be at greater risk for other immunologic transfusion reactions such as hemolytic reactions, type I hypersensitivity reactions, febrile nonhemolytic transfusion reactions, and posttransfusion purpura (thrombocytopenia). In massively transfused dogs, transfusion reactions consisting of fever, vomiting, facial swelling, and delayed hemolysis were noted in 40% of cases, well in excess of the hospital average.[8]

160.10 NONIMMUNOLOGIC TRANSFUSION REACTIONS

Other potential nonimmunologic complications of massive transfusions include bacterial contamination of stored blood, infectious disease transmission, and hyperammonemia. Blood is an excellent bacterial growth medium, and contamination may result from improper collection or handling techniques.

Transfusion of contaminated blood can cause signs that may be difficult to distinguish from transfusion reactions, including fever, vomiting, hypotension, hemolysis, and death. Infectious disease transmission following transfusion is of major concern in human medicine because of human immunodeficiency virus, hepatitis, and other viral infections. The incidence of disease transmission in veterinary patients is not known, but the transmission of blood-borne pathogens like *Ehrlichia, Babesia,* and *Leishmania* is possible following transfusions in dogs.[33,34] Ammonia levels in stored blood rise significantly with time, so patients who receive large volumes may theoretically be at risk for hyperammonemia. Although this has not been a problem in healthy patients, those with severe liver disease or hypoperfusion secondary to shock may not be able to metabolize or excrete this ammonia and may consequently be at greater risk.[35]

160.11 RECOMMENDATIONS FOR MANAGEMENT

Hypothermia, metabolic acidosis, and coagulopathy have all been associated with increased mortality in human patients. Thus one of the priorities in management of massively transfused patients should be the recognition and arrest of this vicious cycle. Rapid resuscitation, measures to prevent cooling, and aggressive rewarming techniques should be employed to minimize hypothermia and acidosis. Useful techniques for temperature control include fluid warmers, warm air blankets, administration of warmed blood products, and admixture of blood products with warmed saline in a 1:1 ratio.

Surgical management of hemorrhage is critical, but initial surgical procedures should be aimed at “damage control” rather than definitive repair, to minimize the impact of hypothermia and acidosis associated with prolonged anesthesia. Using a staged laparotomy approach, sources of hemorrhage or contamination are initially controlled or packed off and the patient is then recovered. Completion of surgical procedures may be performed once cardiovascular status and coagulation have returned to acceptable levels.

To facilitate rapid identification and treatment of coagulation abnormalities, coagulation testing both before and during massive transfusion is recommended. Point-of-care testing for coagulation and electrolyte and acid-base status is a useful tool in these patients, because samples sent to a laboratory rarely provide timely information. Transfusion of fresh frozen plasma should be considered for patients with prolonged PT or aPTT consistent with coagulopathy. Platelet concentrates, if available, may be administered to patients with platelet counts of less than 50,000 cells/μl.

Abnormalities in electrolyte concentrations are nearly universal following massive transfusion, so careful monitoring is recommended, particularly if muscle tremors, hypotension, or arrhythmias are detected. Clinical signs may be difficult to recognize in an anesthetized patient, and a prolonged QT interval on an electrocardiogram or unexplained hypotension may be the first warning of a problem. Treatment with 0.5 to 1.5 ml/kg IV calcium gluconate (10%) is recommended if ionized calcium levels are less than 0.8 mmol/L, or when clinical signs are present.

160.12 OUTCOME

Despite the expectation that injuries necessitating massive transfusion are likely to be associated with a poor outcome, and despite the many associated risks, human and veterinary studies demonstrate that patients with exsanguinating injuries can be treated successfully. Survival rates of 25% to 60% in the veterinary and human literature, and a good functional outcome in most survivors, justify the high cost of acute care in these patients.[3,8]

160.13 SUGGESTED FURTHER READING*

LA Jutkowitz, EA Rozanski, J Moreau, JE Rush: Massive transfusion in dogs: 15 cases (1997-2002). *J Am Vet Med Assoc*. **220**, 2002, 1664, *A small-scale retrospective study addressing clinical indications, complications, and outcome in massively transfused veterinary patients.*

JR Stegman, AJ Birkenheuer, JM Kruger, et al.: Transfusion-associated *Babesia gibsoni* infection in a dog. *J Am Vet Med Assoc*. **222**, 2003, 959, *Documents the transmission of infectious disease through blood transfusion*.

* See the CD-ROM for a complete list of references

161 Chapter 161 Pain and Sedation Assessment

Sandra Z. Perkowski, VMD, PhD, DACVA

161.1 KEY POINTS

- Pain is considered the fifth vital sign in human medicine, emphasizing the importance of an effective approach to pain management in the critical care patient.
- Assessment of pain in the veterinary patient is inherently difficult, especially in the confines of a hospital setting where anxiety and stress can confound the assessment of changes in patient status.
- Physiologic changes, although an integral part of the overall patient assessment, are not always reliable indicators of pain.
- Observational measures of behavior are an essential part of pain assessment, although they are subject to misinterpretation, especially in the anxious or dysphoric patient.
- No single pain scoring system has been universally adopted in veterinary medicine as the gold standard, although many systems have been published and some have been validated.
- Before implementing any assessment tool, it is important to recognize the limits of the technique.
- The effectiveness of analgesic treatment should be reevaluated regularly to help guide pain management.
- A return to normal behavior and/or improvement in quality of life are the ultimate goals of any pain management strategy.

161.2 INTRODUCTION

Analgesics have become increasingly popular in small animal practice, as the awareness of pain and its detrimental effects has increased. Traditionally, it was thought that some pain persisting into the postoperative period may be helpful, to encourage immobility and, in turn, healing and recovery. Similarly, acute pain occurring at the injured area in the trauma patient can serve to help protect the body part or system, minimizing further injury and aiding repair.

However, it is now recognized that acute pain causes a number of significant negative endocrine and metabolic side effects that can actually delay recovery and that far outweigh any potential benefits. These include immobility, decreased pulmonary function with atelectasis, decreased immune function, an increased incidence of pneumonia, catecholamine release and increased oxygen consumption, increased blood pressure and heart rate, peripheral vasoconstriction, stress hormone release, inappetence, and insomnia. Most importantly, pain leads to suffering. Analgesia is especially important for critically ill patients in which any negative physiologic effects may have a profound impact on outcome. Although analgesia may be postponed for a severely injured patient due to the need for immediate, lifesaving interventions, adequate pain control is ultimately essential to offset further detrimental effects.

161.3 DEFINITION OF PAIN

Pain has been defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”[1] By definition, then, pain is a subjective event and cannot truly be measured by an objective observer.

The perception of pain and response to a noxious stimulus is determined not only by the degree of injury, but also the individual's unique experience. Pain assessment becomes inherently more difficult in veterinary patients as a result of the obvious limitations of verbal communication, with attempts to anthropomorphize the animal's behavior, which increase the degree of error in our assessment. As a result, a number of assessment techniques have been published in the veterinary literature over the past several years, some of which are undergoing validation using strict criteria.

In contrast, nociception involves the series of electrochemical events that start at the site of tissue injury and result in the perception of pain. These events can be monitored, measured, and quantified in an experimental setting. Nociception generally involves four distinct processes:

1. Transduction of the noxious stimulus (mechanical, thermal, or chemical) into an electrical stimulus
2. Transmission of the nervous impulse by the primary afferent sensory fibers (nociceptors) from the periphery, through the spinal cord and ascending relay neurons in the thalamus, to the somatosensory cortex
3. Modulation (amplification or inhibition) of the message within the dorsal horn as it ascends
4. Integration of the above processes with the unique psychology of the individual, resulting in the final perception of pain

In addition, the processes involved in the perception of pain are no longer viewed as a static system. Long-term changes occur within the peripheral and central nervous systems following noxious stimulation, that then alter the body's response to further sensory input.

161.4 PAIN VERSUS STRESS

In general, physiologic and behavioral responses to pain have been used to develop a number of assessment tools or rating scales to determine the level of pain and/or sedation in the veterinary patient. These scales may change depending on the circumstances under which they are used (e.g., acute pain following trauma or surgery versus chronic pain of orthopedic or neuropathic origin), the underlying disease process (e.g., cancer versus orthopedic disease), and the location (somatic versus visceral, deep versus superficial) or severity of the inciting stimulus.

It is important to recognize that these pain scoring systems have little value in optimizing our analgesic therapy unless the person implementing them has a basic understanding of pain physiology and pathways. Understanding mechanisms of pain transmission and antinociceptive mechanisms allows a logical choice in prescribing analgesics for our patients. Analgesia may be directed toward minimizing inflammatory changes at the site of injury, inhibiting transduction or transmission of the nociceptive signal (both at peripheral and spinal endings), or increasing the activity of descending inhibitory pathways acting at the central nervous system. For example, opioids have traditionally been viewed as centrally acting drugs and most frequently are given systemically. However, they may also be given epidurally or intrathecally, stimulating opioid receptors found at the level of the spinal cord to produce analgesia. In addition, there is now evidence for the action of endogenous opioids on peripheral sites following tissue damage.

Opioid receptors are manufactured in the cell body (dorsal root ganglion) and transported not only toward the central terminal in the dorsal horn, but also toward the periphery. These peripheral receptors then become active following tissue damage or chronic inflammation (e.g., within the joint capsule). This has led to an interest in the peripheral administration of opioids, such as intraarticular administration of morphine in dogs following cruciate ligament repair.

Another confounding factor in assessing pain in our veterinary patients is that it is frequently accompanied by stress and anxiety. The stress response may occur in the absence of injury and in response to any number of environmental factors, including restraint, new surroundings, the presence of other animals, or other perceived threat to the animal. As anxiety increases the stress response to a painful stimulus, the response itself begins to negatively affect the individual. Such responses include behavioral changes associated with “fight or flight”; neuroendocrine responses including cortisol release, hyperglycemia, and catecholamine release; and physiologic changes associated with sympathetic nervous system stimulation (e.g., tachycardia, hypertension, vasoconstriction), immunosuppression, and hypercoagulability.

In terms of pain assessment, many of the physiologic changes seen during the stress response are similar to those seen in the pain response. The patient may not eat nor sleep well and, in conjunction with the neurohormonal responses, this sets up an overall catabolic state. Although it is incumbent upon the medical provider to treat the animal on the assumption that it may be in pain, frequently it is not possible to quiet the animal using analgesics alone and a sedative agent such as diazepam, midazolam, acepromazine, or low-dose α_2-agonist must be added to reduce the anxiety and allow the animal to rest and recuperate.

161.5 PAIN ASSESSMENT

161.5.1 Behavior

As stated previously, the perception of pain is clearly a subjective experience and can be quite difficult to quantify, especially in veterinary patients. However, some basic strategies can be followed to help in assessing pain in these patients. First of all, it is important to observe the patient both on its own and while interacting with people. Is the patient displaying one or more signs indicative of pain? This includes both physiologic signs associated with sympathetic nervous system stimulation and behavioral signs (Box 161-1).

161.5.1.1 Box 161-1 Signs Associated With Acute Pain in Dogs and Cats

161.5.1.1.1 Physiologic Signs

Increased heart rate with or without arrhythmias

Increased respiratory rate (often with decreased tidal volume)

Increased blood pressure

Increased temperature

Salivation

Dilated pupils

161.5.1.1.2 Behavioral Signs

Vocalization (dog: growling, whining, whimpering, groaning; cat: purring, growling)

Restlessness, agitation

Resents handling of area

Depression, inactivity

Insomnia, reluctance to lie down

Inappetence

Increased aggression or timidity

Abnormal posturing (hunched, prayer position)

Alterations in gait (disuse, guarding)

Licking or chewing at painful area

Trembling, increased muscle tension

Facial expression (fixed stare, squinting)

Failure to groom (cat)

Increased or decreased urination, failure to use litter box (cat)

It is apparent that physiologic responses related to catecholamine release and sympathetic nervous system stimulation may be very difficult to differentiate from changes seen in response to anxiety. Therefore physiologic changes are not always reliable indicators of pain. In one study comparing subjective and objective measures to determine the severity of pain after cruciate ligament repair in dogs,[2] changes in physiologic parameters did not correspond well to pain threshold testing and corresponded poorly with a subjective measure of pain (visual analog or numeric rating scale [see Tools section]). Similar findings have been reported by others in both children[3] and dogs.[4] In addition, pain produces other neuroendocrine responses similar to those produced during other stressful situations, including stress hormone (cortisol) release and hyperglycemia. Furthermore, immunocompetency is decreased and a stress leukogram may be present.

Observational measures of behavior are also an essential part of pain assessment, although they are subject to limitation, especially in the anxious or dysphoric patient. Most people tend to focus on vocalization and agitation as signs of pain. Unfortunately, these two behaviors are frequently the least specific, especially after administration of opioid analgesics or during the postoperative period when many animals are disoriented or excited as a result of the anesthetic drugs that were administered. Many animals will show few outward clinical signs of pain in the presence of other animals or humans.

Species, breed, and age of the animal may also affect the clinical signs exhibited. For example, cats are especially difficult to assess for pain. Analgesics are frequently overlooked in feline patients, because they tend not to vocalize. One study examining analgesic use in dogs and cats after major surgery in a veterinary teaching hospital[5] found that only 1 in 15 cats received any postoperative analgesia and that only one dose of medication was administered. Although much has changed over the ensuing years, it demonstrates how easy it may be to confuse pain with depression in feline patients. Most cats will merely sit quietly in the back of the cage and not move when they are in pain. They frequently stop grooming. They may be inappetent, insomnolent, or mildly pyrexic. A dramatic improvement in attitude and appetite may be seen after the administration of analgesics.

161.5.2 Tools

A number of pain scoring systems are in use in both human and veterinary medicine. The large number of these systems indicates that no one system has been universally adopted as the gold standard. It also should be recognized that pain scales used in the acute setting may not be appropriate for use in the chronic setting, where owner involvement and quality-of-life assessment become increasingly more important.[6]

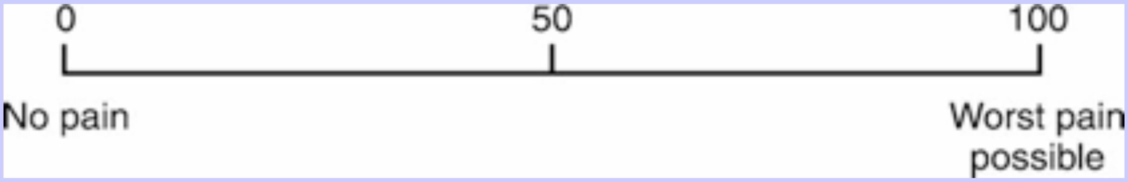
However, a pain assessment form may be helpful in raising awareness to an individual patient's pain and/or distress and increasing the use of appropriate analgesia and/or sedation in the hospital setting. In the acute setting, quantification of pain behaviors is often done using variations of a simple descriptive scale (SDS), a visual analog scale (VAS), or a numeric rating scale (NRS), which may or may not incorporate changes in physiologic parameters.

The SDS typically rates pain as none, mild, moderate, or severe. Each rating is then assigned a number (e.g., from 1 to 4) that becomes the patient's score. Although relatively simple to use, it lacks sensitivity because of the relatively small number of categories. In contrast, a human study found that a 10- to 20-point scale was required to provide sufficient sensitivity to assess pain intensity in a group of patients with chronic pain.[7]

Visual analog (Figure 161-1) and numeric rating scales have been used to evaluate pain in human infants, laboratory animals, and in a number of veterinary clinical studies. These scales can give reproducible results, even when used by multiple observers.[2,8] In pediatric medicine, a strong correlation exists between ratings provided by patients and ratings of their caregivers, using either scale.[9]

The VAS is typically a straight line, 100 mm in length. One end of the line (0 mm) represents no pain and the other end (100 mm) represents the worst pain possible. The observer (or patient) is asked to mark where along the scale the patient's perceived pain would fall and a measurement is then taken and a number recorded, allowing the observer to track changes.

Figure 161-1 Example of a visual analog scale used to assess severity of pain by making a mark along a 100-mm line to represent the patient's estimated level of pain.



Advantages of the VAS are that it avoids the use of descriptive terms and the need to assign a number to the pain. In the hands of an experienced observer, it can be both a sensitive and reproducible assessment tool and has been considered the gold standard pain measurement tool in humans.[10] Similarly, owners can easily be taught to track changes in their animal at home.

Disadvantages of the technique include observer variability in the interpretation of the term *worst pain possible*. For example, does this mean the worst pain possible for this particular injury or disease or for any injury or disease? Another disadvantage is that the VAS may be unduly influenced by signs that are easily detectable. For example, one study found that VAS scores were significantly and consistently correlated with increases in vocalization and respiratory rate in dogs after cruciate ligament repair, both of which are easy to recognize at a quick glance.[2,11] Although both of these signs may increase in response to pain, they may also increase in response to anxiety or drug-induced dysphoria. These other factors must then be identified and taken into account when using a VAS. Similarly, the clinical significance of a given amount of change in the VAS may vary depending on the patient and the disease process. Therefore it is often used in conjunction with other pain assessment tools.

The NRS consists of multiple categories with which to evaluate the patient's behavior. Within each category, levels of that behavior are given and assigned a whole number. In addition to the behaviors used in the NRS, changes in physiologic parameters may be included. For example, an increase in heart rate or respiratory rate from 0 to 10% of baseline in the postsurgical patient may be assigned a 0, a change of 10% to 20% a 1, from 20% to 30% a 2, and so forth, and these scores added to the total. However, it should be noted that multiple studies have shown that changes in heart rate, respiratory rate, and blood pressure correlate poorly or not at all with pain threshold or subjective measures of pain in dogs in the postoperative setting.[2,12] A simple NRS is shown in Table 161-1.

One disadvantage of the NRS is that it is an ordinal measurement and assumes that a change from 1 to 2 is equivalent in degree to a change from 2 to 3. Similarly, the categories themselves are not weighted and instead are assigned equal importance to the overall score. Another problem with the simple descriptors used in some

NRS systems is their lack of specificity. In an unpublished survey involving the clinically active veterinarians and nurses at the University of Pennsylvania (SZ Perkowski, unpublished data, 1992), vocalization was the most commonly cited indicator of pain in animals. However, vocalization also occurs nonspecifically and with a high incidence in the postsurgical patient and can contribute to a falsely high pain score.

Table 161-1 Example of a Numeric Rating Scale Used to Assess Severity of Pain in Dogs

Observation	Score	Criteria
Vocalization	0	No vocalizing
	1	Vocalizing, responds to calm voice and stroking
	2	Vocalizing, does not respond to calm voice and stroking
Movement	0	None
	1	Frequent position changes
	2	Thrashing
Agitation	0	Asleep or calm
	1	Mild agitation
	2	Moderate agitation
	3	Severe agitation

Clearly, behavioral changes indicative of pain may be difficult to recognize in the acute clinical setting. One study comparing reliably the use of an NRS and a quantitative behavioral scoring system over a 24-hour period found that dogs receiving adequate opioid analgesia following ovariohysterectomy had a more rapid return to normal greeting behaviors than dogs that received placebo.[13] However, the NRS failed to differentiate between the two groups of dogs.

A pain scoring system developed by the University of Melbourne (University of Melbourne Pain Scale) to assess postoperative pain in dogs compared preoperative and postoperative behavior and found an improved degree of interobserver agreement using this method.[14] This suggests that increased familiarity with the animal can help with overall pain assessment and management. Another group at the University of Glasgow has more recently validated a composite measure pain scale for use in dogs with acute pain.[15,16] This tool takes the form of a questionnaire, and the behaviors included in the scale are based on seven categories: posture, comfort, vocalization, attention to wound, demeanor, mobility, and response to touch.

161.6 CONCLUSION

Veterinary patients frequently require analgesics after acute trauma or surgery. Before implementing any assessment tool, it is important to recognize the limits of the technique. Learning to anticipate when a patient will be in pain is extremely helpful, because pain is much easier to manage if the patient is treated before experiencing pain and upset than if treatment is initiated afterward. Frequently, knowing the patient's underlying disorder, whether or not a procedure has recently been performed and, if so, what type will guide the use of analgesic drugs.

Usually analgesics are given before an invasive procedure to provide preemptive analgesia and minimize "wind-up." Remember that very young, very old, and critically ill patients tend to be less tolerant of pain and the neurohormonal and autonomic changes associated with pain. Close attention should be paid as to whether the initial treatment provides adequate analgesia and how long the analgesic effect lasts. Reevaluate the effectiveness of treatment regularly.

Response to analgesic therapy can help enormously in guiding overall pain treatment. Do not wait for obvious signs of pain before repeating the intervention, unless the side effects are excessive. Individualize the management approach. Before administering any drug, carefully observe the animal and consider the underlying disease process. If anticipated side effects are undesirable or potentially life threatening, the analgesia technique should be modified. It is important to remember that a return to normal behavior is the ultimate goal of pain management.

161.7 SUGGESTED FURTHER READING*

MG Conzemius, CM Hill, JL Sammarco, SZ Perkowski: Correlation between subjective and objective measures used to determine severity of postoperative pain in dogs. *J Am Vet Med Assoc*. **210**, 1997, 1619, *One of the first veterinary studies to look at correlations among several methods used to determine the severity of postoperative pain in dogs, including physiologic parameters, a pain threshold measurement, VAS, and NRS. Weak association was found among the techniques, although a high agreement was found among observers for the NRS and VAS*.

AM Firth, SL Haldane: Development of a scale to evaluate postoperative pain in dogs. *J Am Vet Med Assoc*. **214**, 1999, 651, *Paper describing development of a scale using both physiologic and behavioral responses, the University of Melbourne Pain Scale, commonly used by many veterinarians today*.

B Hansen, E Hardie: Prescription and use of analgesics in dogs and cats in a veterinary teaching hospital: 258 cases (1983-1989). *J Am Vet Med Assoc*. **202**, 1997, 1485, *A retrospective study showing that only 40% of dogs and only one cat received any analgesia postoperatively at a veterinary teaching hospital over a 6-year period; vocalization was the most common indicator of pain cited by clinicians for analgesic use. A wake-up call for many veterinarians prescribing analgesics for postoperative pain; helped incite the widespread institution of pain assessment education to the veterinary community*.

L Holton, J Reid, EM Scott, et al.: Development of a behaviour-based scale to measure acute pain in dogs. *Vet Rec*. **148**, 2001, 525, *A paper that describes the development and validation of the Glasgow Composite Pain Tool, a questionnaire made up of several questions organized into seven categories: demeanor and response to people, posture, mobility, activity, response to touch, attention to painful area, and vocalization*.

KVB Yazbek, DT Fantoni: Validity of a health-related quality-of-life scale for dogs with signs of pain secondary to cancer. *J Am Vet Med Assoc*. **226**, 2005, 1354, *A good study, emphasizing the importance of validating quality-of-life scales or other questionnaires used for pain assessment in animals*.

* See the CD-ROM for a complete list of references

162 Chapter 162 Sedation of the Critically ill Patient

Sandra Z. Perkowski, VMD, PhD, DACVA

162.1 KEY POINTS

- Evaluation and preparation of the critically ill patient are essential before administering any drug, because preexisting conditions and patient management during this period will determine the extent of crises.
- The choice of sedative agent will depend on the patient's current physical status, reason for hospitalization, pertinent history, and the procedure to be performed.
- Most sedative techniques in the critically ill patient, especially those with cardiovascular compromise, involve using a sedative or tranquilizer in combination with an opioid analgesic.
- The respiratory and cardiovascular effects of the various sedative agents should be considered carefully before administration.

162.2 INTRODUCTION

Sedation of critically ill veterinary patients is often required to permit minor surgical procedures and diagnostic techniques. Advantages over general anesthesia include flexibility and ease of drug administration, while avoiding the need for intubation and inhalant anesthetics. Significant cardiovascular and respiratory depression may result, however, leading to life-threatening patient compromise. To minimize the influence of preexisting conditions and the extent of crises that may occur, evaluation and adequate preparation of the patient are essential before administering any drug.

162.3 PATIENT EVALUATION AND MANAGEMENT

On presentation, immediate attention should be paid to the ABCs (airway, breathing, circulation; see Chapter 2, Patient Triage). These should be deemed adequate before proceeding. Evaluation of neurologic status, including mental status and evidence of spinal cord or head trauma, should be included. A complete history should be obtained if possible, including presenting complaint, known medical conditions, any current medications, and previous anesthesia history.

Oxygen supplementation and ventilatory support are provided as necessary. Indications for securing an airway early include poor ventilation or oxygenation, deteriorating mental status, lack of a gag reflex, or upper airway obstruction. Stabilization of fluid balance and cardiovascular function are also essential before drug administration, although assessing the adequacy of intravascular volume can be difficult. Inadequate intravascular volume is aggravated by the peripheral vasodilation caused by many pharmacologic agents and the generalized decrease in sympathetic tone and attenuation of compensatory mechanisms that occur with sedation. Adequate intravascular access is extremely important.

Cardiac arrhythmias, especially premature ventricular contractions (PVCs), are seen commonly in critically ill patients, including those with gastric dilation-volvulus, hemoabdomen, and/or thoracic trauma. In addition, they can occur secondary to electrolyte abnormalities, hypoxemia, or hypercarbia. The type and significance of arrhythmias should be determined and the underlying cause treated, if possible. Indications for antiarrhythmic therapy before drug administration include frequent multiform PVCs or paroxysmal ventricular tachycardia that adversely affects blood pressure (see Chapter 47, Ventricular Tachyarrhythmias).

When time and the animal's condition permit, electrolyte abnormalities should be normalized before drug administration. Severe hyperkalemia (potassium >6 mmol/L) is seen frequently in patients with renal compromise, urinary tract obstruction or rupture, massive tissue trauma, or severe dehydration with metabolic acidosis (see Chapter 55, Potassium Disorders). Drug administration in a patient with hyperkalemia is associated with a high incidence of arrhythmias and cardiac arrest, and therefore appropriate treatment should be instituted before proceeding. Hypocalcemia may be seen transiently after citrated blood product administration, although this generally self-resolves.

162.4 CHOICE OF AGENT

The choice of sedative agent will depend on the patient's current physical status, reason for presentation, pertinent history, and the procedure to be performed. Special attention should be paid to both cardiovascular and respiratory effects of these agents, but contraindications to drug use should also be considered. Intravenous administration allows for titration of the drugs and is generally preferred. Intramuscular sedation may be helpful, especially in the fractious patient or one with severe respiratory distress that becomes easily stressed with restraint. A complete list of commonly used sedative drugs can be found in Table 162-1.

162.4.1 Opioids

Most sedative techniques in the critically ill patient involve a sedative or tranquilizer in combination with an opioid analgesic (see Chapter 184, Narcotic Agonists and Antagonists). This neuroleptanalgesic combination generally produces a greater degree of sedation and analgesia with less cardiovascular depression than that achieved by comparable doses of either drug alone.

Most of the clinically used pure opioid agonists (morphine, methadone, oxymorphone, hydromorphone, fentanyl) bind primarily to the μ-receptor in the central nervous system, although they interact with the other receptors (κ, δ), especially at higher dosages.[1] In healthy animals, opioids cause behavioral changes ranging from sedation to excitement; however, in critically ill patients, opioids usually cause sedation. Cardiovascular function, including left ventricular function, cardiac output, and systemic blood pressure, is well maintained. Vagally mediated bradycardia may be seen and can be treated with anticholinergic agents (atropine, glycopyrrolate), if necessary. Oxymorphone, hydromorphone, and fentanyl are particularly useful intravenous agents, especially in combination with benzodiazepine tranquilizers (midazolam, diazepam), because they provide the most cardiovascular stability.[2,3] Histamine release with subsequent vasodilation and hypotension may occur after meperidine or morphine administration.[4]

Table 162-1 Commonly Used Sedative Drug Dosages

Drug	Dosage (mg/kg)	Route
Anticholinergic Agents		
Atropine	0.02	IM, SC
	0.01	IV
Glycopyrrolate	0.01	IM
	0.005	IV
Sedatives and Tranquilizers		
Acepromazine	0.005 to 0.1	IM, IV, SC
Diazepam	0.2 to 0.5	IM, IV
Midazolam	0.1 to 0.5	IM, IV
Flumazenil (reversal agent)	0.01 to 0.02	IV
Medetomidine	0.001 to 0.03	IM
Atipamezole (reversal agent)	0.1 to 0.25	IV, IM
Opioid Agonists and Partial Agonists		
Buprenorphine	0.005 to 0.02	IM, IV
Butorphanol	0.1 to 0.5	IV
	0.2 to 0.5	IM
Fentanyl	0.025 to 0.01	IV
Hydromorphone	0.05 to 0.2 (½ dose in cats)	IM, IV
Morphine	0.2 to 2 (½ dose in cats)	IM, IV
Methadone	0.1 to 0.5 (½ dose in cats) 0.2 to 2.0 (½ dose in cats)	IV SC, IM
Nalbuphine	0.1 to 2.0	IM, IV
Oxymorphone	0.02 to 0.2 (½ dose in cats)	IM, IV
Naloxone	0.01 to 0.04	IV, IM (reversal agent)
Other Agents		
Ketamine	2 to 8 (cat only)	IM
	2 to 5	IV
Telazol	2 to 4	IM (may have prolonged recovery)
Propofol	1 to 6	IV (titrate slowly to effect)

IM, Intramuscular; *IV,* intravenous; *SC,* subcutaneous.

Although opioids are relatively sparing of the cardiovascular system, they may act as respiratory depressants, causing a decreased ventilatory response to hypercarbia. Respiratory depression may be exacerbated by concomitant administration of other sedatives. Therefore opioids should be used judiciously and at decreased dosages if respiratory depression and hypoventilation are contraindicated, as in cases with upper airway obstruction or increased intracranial pressure. Materials for intubation and positive-pressure ventilation should be readily available before drug administration in these patients. Do not mistake panting, a common side effect of opioids, with effective ventilation; look carefully at the depth of each breath, the rate of respiration, and the arterial carbon dioxide level, if indicated.

Butorphanol, a κ-agonist and μ-antagonist, or buprenorphine, a partial μ-agonist, may cause less respiratory depression and be preferable in some critically ill cases. Other clinically significant side effects such as vomiting and decreased gastrointestinal motility may also be less pronounced with these drugs, although they tend to provide less analgesia. If undesirable side effects should occur, the opioid can be reversed using naloxone (0.01 to 0.02 mg/kg IV, IM, or SC). Buprenorphine may be difficult to reverse and require up to 10 times the normal naloxone dosage. Opioid reversal with naloxone will also remove the analgesic effects, and this should be anticipated by the clinician. Alternatively, small doses of butorphanol (0.05 mg/kg IV) or nalbuphine (0.05 mg/kg IV) may be titrated to reverse some of the sedative effect of a pure opioid agonist, while retaining some of the analgesia by enhancing the κ effects.

Table 162-2 Suggested Dosages for Opioids in Small Animals

Drug	Dosage (mg/kg)	Route	Duration (hr)	Comments
Opioid Agonists *				May cause excitement with IV use
Morphine	0.1 to 0.5 (dog)	IV	2 to 4	May cause hypotension with IV use
	0.2 to 2 (dog)	IM, SC	2 to 6	Vomiting may occur
Methadone	0.1 to 0.5 (½ dose in cats) 0.2 to 2.0 (½ dose in cats)	IV SC, IM	4 to 6	Causes less sedation and vomiting than morphine
Oxymorphone	0.02 to 0.2	IV	1 to 4	Good CV stability
	0.05 to 0.2	IM, SC	2 to 6	
Hydromorphone	0.05 to 0.2	IM, IV	1 to 4	Good CV stability
Fentanyl	2 to 10 μg/kg CRI: 20 to 100 μg/kg/hr	IV	—	Intraoperatively
	2 to 5 μg/kg/hr	IV	—	Postoperatively
Opioid Agonist/antagonists or Partial Agonists				
Butorphanol	0.1 to 0.5	IV, IM, SC	2 to 6	κ-Agonist μ-Antagonist
Nalbuphine	0.1 to 2	IV, IM, SC	0.5 to 1	Same as butorphanol
Buprenorphine	0.005 to 0.02	IV, IM, SC	4 to 12	Mu partial agonist Oral absorption excellent (cat) May be difficult to reverse

CRI, Constant rate infusion; *CV,* cardiovascular; *IM,* intramuscular; *IV,* intravenous; *SC,* subcutaneous.

Before administering an opioid (or any other drug), the veterinarian should carefully observe the animal and consider the underlying disease process. Commonly used opioid drugs and their pertinent information can be found in Table 162-2.

* Cat dosage is generally half of what is used in dogs for any of the above opioids. Cats may be more prone to excitement after opioid administration.

162.5 SEDATIVES AND TRANQUILIZERS

162.5.1 Benzodiazepines

Benzodiazepines (diazepam, midazolam) are mild tranquilizers and cause minimal cardiopulmonary depression (see Chapter 185, Benzodiazepines).[5] They are not generally used alone for sedation, because the result is often unpredictable and the animal may become difficult to handle. They are most commonly given in combination with other drugs to increase their effect. Both drugs have similar effects and are given at similar dosage ranges (0.2 to 0.5 mg/kg IV or IM), although midazolam is preferred for IM use because it is water soluble and readily absorbed. In critically ill patients, small IV doses of either drug can cause profound sedation. In addition, diazepam is metabolized to active metabolites that can cause a prolonged duration of action in some animals.[6] These effects are readily reversed using the benzodiazepine antagonist flumazenil.

162.5.2 Phenothiazines

Phenothiazine tranquilizers (acepromazine) are commonly used in healthy veterinary patients to provide a calming effect.[7] They are generally avoided when volume status or cardiovascular stability is a concern, however, because they act as α-antagonists, causing peripheral vasodilation and potentially severe hypotension in hypovolemic patients.

Acepromazine may be useful in animals with upper airway obstruction when calming of the patient may decrease respiratory effort and actually improve ventilation. Respiratory depression is minimal and intramuscular administration is usually effective if given sufficient time to work (20 to 30 minutes after injection). Acepromazine should be used at lower dosages (0.005 to 0.02 mg/kg IV or 0.01 to 0.05 mg/kg IM), especially if the physical examination has been difficult to perform because of the animal's degree of respiratory distress.

162.5.3 α_2-Agonists

α_2-Agonists (xylazine, medetomidine, dexmedetomidine) produce sedation, muscle relaxation, and analgesia.[7] They are not generally recommended for use in critically ill patients because of the profound changes in cardiac output and blood pressure that occur after their administration and the availability of other cardiovascular-sparing drugs. Cardiac output decreases after drug administration because of a decreased heart rate, direct myocardial depression, and increased afterload (decreased stroke volume). In addition, coronary vasoconstriction can lead to myocardial hypoxia and dysfunction. Several surveys have suggested that xylazine use is associated with a higher incidence of morbidity and mortality than other anesthetic agents.[8,9]

Medetomidine is more specific for the α_2-receptor (versus the α_1-receptor) than is xylazine. However, the adverse cardiovascular effects are mediated by the effects on the α_2-receptor. In addition, the effects of medetomidine last longer than those of xylazine. Notable side effects include significant bradycardia (heart rate <40 beats/min with or without atrioventricular block) and intense peripheral vasoconstriction (with pale, white mucous membranes). Administration of an anticholinergic drug either in combination with the α_2-sedative or as a treatment for bradycardia is not recommended, because it provides only a minimal increase in cardiac output in concert with an increased myocardial workload and increased incidence of cardiac arrhythmias. Reversal of the drug with atipamezole is the preferred treatment. Other side effects of α_2-sedative administration include respiratory depression, vomiting, inhibition of insulin release (hyperglycemia), and diuresis.

Recommended dosage ranges for medetomidine (on insert) are 10 to 40 μg/kg IV or IM and are associated with moderate to profound sedation and analgesia. However, hemodynamic changes are qualitatively similar irrespective of the dosage when administered between 1 and 20 μg/kg IV, although a lesser effect is seen at 1 to 2 μg/kg. (NOTE: the effect is near maximal at 5 μg/kg.) Medetomidine (1 μg/kg IV) in dogs decreased cardiac output to less than 40% of resting values and it remained almost 50% below normal for 1 hour.[10] Dexmedetomidine (1 μg/kg) given to anesthetized dogs increased coronary vascular resistance, decreased coronary blood flow in all myocardial layers, and increased myocardial oxygen extraction. Prolonged administration of low-dose medetomidine given as a constant rate infusion (CRI) of 1.5 μg/kg/hr, a rate similar to that commonly suggested for long-term sedation, caused a pronounced decrease in cardiac index and heart rate, increased left atrial blood pressure, and decreased tissue oxygen delivery in healthy young dogs, suggesting the need for further evaluation before recommending its use in critically ill patients.[11]

162.6 OTHER ANESTHETIC AGENTS

162.6.1 Ketamine

Ketamine is a dissociative anesthetic with variable effects on the cardiovascular system, depending on the patient's status. Increases in heart rate, cardiac output, and blood pressure seen with ketamine are caused by a centrally mediated sympathetic response and endogenous catecholamine release.[12] Because of the potential for causing increased myocardial contractility and oxygen consumption, ketamine should be used only after careful consideration in patients with underlying cardiac disease (e.g., hypertrophic cardiomyopathy). Catecholamine release may also predispose to arrhythmias. Ketamine has a direct myocardial depressant effect and, in debilitated patients with a poor catecholamine response, destabilization of the cardiovascular system and hypotension may occur.

Although ketamine causes a dosage-dependent respiratory depression, this is usually transient and ketamine may be useful when maintenance of spontaneous ventilation is desirable. It also possesses bronchodilator activity that may be beneficial for patients with bronchoconstriction. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist and may be a useful adjunct to other analgesic therapy. Best results have been found in peripheral or somatic pain models, although visceral pain is partially abolished. Ketamine increases both intracranial and intraocular pressure and is therefore contraindicated in patients with head or ocular hypertension or trauma.

Ketamine has a rapid onset of action after intramuscular injection and is often used for intramuscular sedation in cats. Ketamine is rarely used intramuscular in dogs and should not be used alone because it may cause seizure-like activity. More commonly, ketamine is administered intravenously, generally given in combination with diazepam (or another tranquilizer) to minimize the possibility of ketamine-induced seizures and muscle rigidity. Ketamine is metabolized by the liver in most species other than the cat, in which the drug is eliminated unchanged by the kidney. Dosage should be adjusted accordingly in patients with liver or renal disease. When faced with a recalcitrant feline patient for which sedation is required, but a decrease in ketamine dosage is desired, a combination of ketamine (2 to 6 mg/kg), oxymorphone (0.05 mg/kg) or hydromorphone (0.1 mg/kg), and midazolam or diazepam (0.2 to 0.5 mg/kg) provides excellent restraint.

162.6.2 Propofol

Propofol is an ultrashort-acting intravenous anesthetic with a 5- to 10-minute duration of anesthesia after induction, with the patient being remarkably alert on recovery. Because of its short duration of action, it is ideal for short procedures and sedations. Propofol is a peripheral vasodilator and myocardial depressant and may cause significant cardiovascular depression in patients that are volume depleted or cardiovascularly compromised.[13,14] Propofol should not be used (or used only after careful consideration) in these cases. Cardiovascular depression is especially pronounced if propofol is given as a large, rapid bolus, so smaller, slowly administered boluses (1 to 2 mg/kg IV) are preferred. Propofol can cause significant respiratory depression, again more pronounced with large, rapid boluses. Animals should receive supplemental oxygen before, during, and after propofol administration (see Chapter 19, Oxygen Therapy).

Propofol may be given in combination with other cardiovascular-sparing drugs, such as opioids or benzodiazepines, which decreases the amount of propofol required for induction. Diazepam (0.2 to 0.5 mg/kg

IV) also helps to control the myoclonic twitching occasionally seen after propofol administration. Propofol can be given as a CRI (0.005 to 0.2 mg/kg/min) for long-term sedation. Cats occasionally will have a prolonged recovery, and Heinz body formation has been reported after repeated propofol sedation in cats.[15] Propofol is provided in a soybean oil and lecithin emulsion and should be handled with strict aseptic technique. The manufacturer states that propofol should not be refrigerated and, once opened, the contents should be used within 6 hours because of the high potential for significant bacterial contamination.

162.7 INDICATIONS

162.7.1 Cardiovascular Instability

Patients with cardiovascular instability include those with primary cardiac disease and those with cardiac signs (e.g., arrhythmias) secondary to trauma or significant metabolic disease. The choice of agent will depend on the underlying disease, the presence or absence and degree of heart failure, and the presence or absence of arrhythmias.

Stress during patient handling should be prevented, if possible, to minimize catecholamine release, tachycardia, and increased myocardial work. If sedation is necessary in a patient with cardiac abnormalities, opioids are generally the drugs of choice. Anticholinergic agents are not used unless indicated. 703 704

A combination of an opioid agonist (e.g., oxymorphone 0.05 to 0.1 mg/kg or hydromorphone 0.1 to 0.2 mg/kg) or agonist/antagonist (e.g., butorphanol 0.1 mg/kg or buprenorphine 0.005 to 0.01 mg/kg), and a benzodiazepine tranquilizer (diazepam 0.25 mg/kg or midazolam 0.2 mg/kg), may be used to sedate patients for chest radiography or echocardiography. This combination provides sedation with minimal cardiovascular depression. Some patients may pant if a pure opioid agonist is used. The dose may be repeated IV, if necessary, or the dosage doubled and given IM.

Reversal may be accomplished by using an opioid antagonist such as naloxone (0.02 mg/kg) and/or a benzodiazepine antagonist such as flumazenil (0.01 to 0.02 mg/kg) intravenoulsy. Phenothiazine tranquilizers such as acepromazine should be avoided in patients when volume status or cardiovascular stability is a concern. However, acepromazine in very low dosages (0.005 mg/kg IV) may be beneficial in some circumstances because it calms the patient, decreases afterload, and decreases the incidence of arrhythmias. It should be used only after careful consideration, however, because the α-blockade may lead to peripheral vasodilation, hypotension, and decreased preload (and there is no reversal agent). α_2-Agonists should be avoided in patients with heart disease and ketamine should be used only after careful consideration.

162.7.2 Respiratory Disease

Respiratory diseases requiring emergency anesthesia include those leading to severe hypoventilation (e.g., upper airway obstruction), hypoxemia (e.g., primary lung disease), or both (e.g., diaphragmatic hernia). Animals will be handled slightly differently depending on whether the primary problem is an inability to ventilate or an inability to oxygenate. Manipulations in both groups should occur with minimal stress or excitement. Most patients will benefit from supplemental oxygen.

All anesthetic agents depress respiration to some degree, and this should be taken into account before administration. Emergency equipment for securing an airway and manually ventilating the patient should be readily available. Respiratory depressants, such as opioids, should be used judiciously in patients with severe hypoxemia or upper airway obstruction. The animal should be monitored closely after administration of any drug.

Premedication with acepromazine is very useful in patients with upper airway obstruction. Low dosages (0.005 to 0.02 mg/kg IM) should be used if a complete physical examination cannot be performed without stressing the patient, although the drug should be given sufficient time to have an effect. Ketamine or propofol also may be used. Patient positioning may be important (e.g., in the patient with diaphragmatic hernia). The least affected side should face upward (or at least try to maintain sternal recumbency) to aid ventilation.

Sedating an animal that cannot breathe due to airway obstruction is among the most potentially catastrophic of all procedures. Never assume that intubation is possible. Have assorted endotracheal tube sizes available (occasionally requiring some ingenuity), stylets, a laryngoscope (ideally), and a tracheostomy set. Potent respiratory depressants should be avoided when intubation may be difficult or impossible. Induction with small boluses of propofol (to minimize respiratory effects) and diazepam (0.2 to 0.5 mg/kg) may be useful. Alternatively, ketamine (2 to 4 mg/kg) and diazepam may be administered. In animals with hypoxemia but no airway obstruction, opioids may be used.

162.8 SUGGESTED FURTHER READING*

JE Ilkiw, PJ Pascoe, SC Haskins, JD Patz: Cardiovascular and respiratory effects of propofol administration in hypovolemic dogs. *Am J Vet Res*. **53**, 1992, 2323, *A laboratory study demonstrating adverse cardiopulmonary effects of an induction bolus of propofol (6 mg/kg IV) given to hypovolemic dogs, previously bled to a mean arterial pressure of 60 mm Hg. Changes include significant decreases in mean arterial pressure, arterial oxygen tension, and pH.*

JC Thurmon, WJ Tranquilli, GJ Benson, Injectable anesthetics: In JC Thurmon, WJ Tranquilli, GJ, Benson (Eds.): *Lumb & Jones' veterinary anesthesia*. ed 3, 1996, Williams & Wilkins, Baltimore, *Generally a good review of basic veterinary anesthesia. Easy to read; a very good review of several anesthetic agents.*

HC Lin: Dissociative anesthetics. In JC Thurmon, WJ Tranquilli, GJ Benson (Eds.): *Lumb & Jones' veterinary anesthesia*. ed 3, 1996, Williams & Wilkins, Baltimore, *Generally a good review of basic veterinary anesthesia. An excellent in-depth review of ketamine effects in a number of species.*

BH Pypendop, JP Vergenstegen: Hemodynamic effects of medetomidine in the dog: a dose titration study. *Vet Surg*. **27**, 1998, 612, *An excellent laboratory study using instrumented dogs showing that various dosages of medetomidine (ranging from 1 to 20 µg/kg IV) resulted in significant and prolonged cardiovascular changes.*

T Reisine, G Pasternak: Opioid analgesics and antagonists. In JG Hardman, LE Limbird (Eds.): *Goodman & Gilman's the pharmacological basis of therapeutics*. ed 9, 1996, McGraw-Hill, New York, *An excellent source for basic pharmacologic information. Some of the earlier editions include drugs still commonly in use in veterinary medicine.*

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* See the CD-ROM for a complete list of references

163 Chapter 163 Anesthesia of the Critically ill Patient

Jane Quandt, DVM, MS, BS, DACVA, DACVECC

163.1 KEY POINTS

- Stabilization of the critically ill animal before anesthesia is imperative to minimize anesthetic complications.
- Anticipate problems and have an appropriate and efficient treatment and therapeutic plan before anesthesia is begun.
- Consider using a balanced anesthesia technique to minimize deleterious effects of single-use drug therapy.

163.2 INTRODUCTION

In the critically ill patient, a thorough preoperative assessment is necessary to define what type of trauma or compromise the patient is undergoing. The critically ill patient has altered physiology and decreased reserves that will affect the pharmacokinetic and pharmacodynamic behavior of anesthetic drugs. These patients benefit from minimizing stress levels and optimizing oxygen delivery.

Stabilization of the critically ill patient before anesthetic drug exposure is essential, because the risks associated with anesthesia in an unstable patient increase the risks of anesthetic complications.

163.3 STABILIZATION

Thorough diagnostic tests should be performed before administering anesthesia, including serial physical examinations, radiographs, blood chemistry, complete blood count, coagulation profile, acid-base status, and blood glucose and lactate levels. A dehydrated or hypovolemic state along with fluid, acid-base, and electrolyte abnormalities should be corrected before anesthesia is begun.

Venous access is imperative in managing and anesthetizing the critically ill patient, because anesthesia-associated hypotension is not uncommon. Intravenous administration of medications is usually preferred, because absorption may be delayed with intramuscular or subcutaneous administration, particularly when the patient is dehydrated, hypovolemic, poorly perfused, or hypothermic. Critically ill patients often benefit from having more than one IV catheter, so that multiple agents and fluids can be given during and after the anesthetic period. Either peripheral or central placement can be used; however, if fluids need to be given at a rapid, shock bolus rate, the shortest, widest bore catheter will allow for the most rapid administration (i.e., peripheral cephalic catheter).

Venous access is also important to provide warm IV fluids before and during anesthesia, to help maintain organ perfusion and body temperature. An IV catheter will provide a port for drug administration, antibiotic delivery, vasopressor and inotropic support, and fluid therapy. A minimum of two intravenous catheters should be placed before anesthesia in unstable patients to accommodate different fluid rates and incompatibilities of various agents, such as vasopressors, sodium bicarbonate, and blood products.

Blood products should be given through a dedicated catheter; no other fluids or drugs should be administered in that line during the transfusion because of concerns for possible contamination and potential for bacterial growth. This is also true for the catheter used for total parenteral nutrition, a dedicated line that should never be disconnected or have any other fluid running through it concurrently because of the risk of sepsis. Total parenteral nutrition contains approximately 70% to 80% free water (depending on the formula). As a consequence only 20% to 30% of the infused volume should be accounted for as part of the crystalloid fluid volume.

An arterial catheter should be inserted once the animal is under general anesthesia. An arterial catheter will allow for direct arterial blood pressure measurement and can be used to collect blood samples for blood gas analysis.

A packed cell volume (PCV) greater than 25% is necessary for adequate oxygen carrying capacity and oxygen delivery.[1] During anesthesia the PCV can decrease by 3% to 5%; therefore even a small volume of blood loss may be significant and may warrant a blood transfusion.[1] Similarly, hypoproteinemic patients (total protein 3.5 g/dl or less and/or an albumin 2 g/dl or less, or both) may benefit from colloids to help maintain normal colloid osmotic pressure (COP) (normal is 18 to 24 mm Hg) and to prevent edema formation or vascular leak.[2,3]

Measurement of COP before anesthesia is helpful in determining the need for colloid support and to help determine when to terminate colloid therapy. If patients are hypoproteinemic, options include hydroxyethyl starch, dextran-70, 25% human serum albumin, or even Oxyglobin. If the patient is small, hypocoagulable, or hypoalbuminemic, fresh frozen plasma (FFP) given at 6 to 20 ml/kg is warranted.

Unfortunately, size, dosing, and cost become limiting factors for the use of FFP to treat hypoalbuminemia in larger patients, because a dose of approximately 45 ml/kg of FFP is required to increase the albumin by 1 g/dl.[4] Hydroxyethyl starch and dextran-70 can both cause a dosage-dependent coagulopathy. Administration of these products should be limited or avoided in patients with known coagulation defects, and the total amount given to any one patient should ideally be limited to less than 20 ml/kg per 24 hours.

Human serum albumin (HAS) 25% has been utilized in veterinary medicine; however, its use has not been well 705 706 researched and side effects such as polyarthritis, future transfusion reaction, glomerulonephritis, and other immune-mediated effects warrant further investigation.[3] If used, this product should be treated as a transfusion, knowing that subsequent reactions may occur.

Finally, patients should be evaluated carefully for underlying metabolic disease before anesthesia, because this may affect the anesthetic protocol. Patients with renal insufficiency may require a higher fluid rate to maintain renal perfusion, and urine output (UOP) should be monitored carefully during anesthesia.[5] In addition, renal drug excretion may be delayed, so these agents should be used cautiously (e.g., ketamine in cats).

In patients with liver disease, anesthesia protocols and monitoring may be affected by decreased glucose production, decreased albumin production, altered drug metabolism via cytochrome P-450 enzymes, and decreased production of clotting factors.[5] Patients with heart disease may be less able to compensate under anesthesia, and fluid overload should be avoided. Blood pressure should also be carefully monitored, because anesthesia-induced hypotension may result in decompensation. Finally, one should always consider preexisting drug therapy, such as nonsteroidal antiinflammatory drugs (NSAIDs), diuretics, anticonvulsants, and cardiac medications.

163.4 PREMEDICATION

Premedication may not be necessary unless the animal is in extreme pain or is vicious. If the critically ill patient would benefit from premedication, opioids such as morphine, hydromorphone, or oxymorphone in combination with a tranquilizer such as midazolam or low-dose acepromazine can be given intramuscularly to provide analgesia and sedation. In the animal that is in extreme pain or is vicious, the μ-agonist narcotic can be combined with the α_2-

agonist, medetomidine (5 to 10 μg/kg IM) for enhanced analgesia, sedation, and restraint. Table 163-1 lists drugs used for anesthesia.

Critically ill patients are often depressed, lethargic, and require minimal drug therapy for induction. Anticholinergic agents are not used routinely unless there is a need to treat bradycardia. Protocols should be implemented to minimize the amount of time the animal is under anesthesia; therefore preparations such as preclipping the surgical site while the animal is still awake should be performed if possible.

Preoxygenation will allow for additional time to intubate the animal; this is especially helpful for those animals in respiratory distress or those with an airway that may be difficult to intubate. Finally, electrocardiography (ECG) and blood pressure monitoring should be in place before induction to detect arrhythmias, hypotension, or cardiovascular collapse that may occur during induction.

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INDUCTION

In the compromised, critically ill patient, anesthetic drug dosages often can be reduced to half of that for a normal, healthy patient. Induction drugs should be titrated slowly intravenously to effect, and the minimal amount necessary to intubate the patient should be used. In addition, a balanced anesthetic technique will help to minimize the side effects that can occur with a single agent. One can consider using local anesthetic blocks and epidurals, if appropriate, to decrease the amount of general anesthesia that is required.

Intubation should always be performed to control the airway, to provide the ability to ventilate the patient, and to protect the airway from aspiration. A laryngoscope, a variety of endotracheal tubes and sizes, and a breathing circuit that matches the patient's size should all be readily available. All supplies and machinery should be checked thoroughly before induction and intubation. One should be ready to implement intermittent positive-pressure ventilation (IPPV) if the patient hypoventilates, becomes apneic, or is to undergo a thoracic procedure.

Ideally, a slow transition to general anesthesia would allow time for the cardiovascular and nervous systems to respond and accommodate.[6] However, the critically ill patient may not be able to respond appropriately, and therapeutic intervention must be available to prevent demise. For example, the patient in respiratory distress will require a rapid-sequence intubation to gain control of the airway and provide ventilation with 100% oxygen.

A rapid-sequence induction can be accomplished with agents that have a short onset, such as thiopental or propofol. These agents have an onset time of approximately 30 seconds and need to be given intravenously. Their duration is also short, with thiopental lasing 10 to 15 minutes and propofol lasting 5 to 10 minutes; propofol may be the preferred agent because of its shorter duration of action.[7] Both of these drugs can be used in combination with diazepam or midazolam to improve relaxation and to decrease the overall dosage needed. Both agents are capable of inducing cardiac arrhythmias, hypotension, and apnea; hence, IPPV may be necessary.[7] Neither agent will provide analgesia, so analgesics must be given (inhalant or injectable agents) before the surgical procedure is begun.

In the critically ill patient with a stable respiratory status, a more gradual induction can be performed. This may be accomplished with neuroleptanalgesic techniques using hydromorphone, oxymorphone, or fentanyl with diazepam or midazolam, with the addition of either propofol or ketamine to facilitate induction. The use of multiple agents (e.g., hydromorphone, diazepam, ketamine, and lidocaine) is an example of balanced anesthesia. This will have a slower onset, but will provide analgesia and is less stressful to the cardiovascular system.[8] Ketamine may be used to enhance analgesia and will increase heart rate and blood pressure.[9]

A drug used for induction serves as a loading dose for a constant rate infusion (CRI). Morphine (3.3 μg/kg/min), lidocaine (50 μg/kg/min), and ketamine (10 μg/kg/min) can be administered as a CRI analgesic combination in dogs.[8] In addition, lidocaine may retard the effects of compromised viscera, reperfusion injury, and ventricular arrhythmias, a result of its free radical scavenging abilities, analgesic effects, and antiarrhythmic properties.[10]

163.6 MAINTENANCE

Once the animal is intubated, anesthesia can be maintained via an inhalant agent such as isoflurane or sevoflurane. These two agents are the most commonly used, but both cause cardiovascular and respiratory depression.[11] Both agents have a rapid onset and recovery time, allowing for rapid change in anesthetic concentration.[11]

Table 163-1 Anesthesic Agents and Their Dosages

Drugs	Comment	Dosage in mg/kg
Anticholinergic agents	May make secretions more viscous	Atropine 0.04 IM, 0.02 IV
	Increase anatomic dead space	Glycopyrrolate 0.01 IM, IV
	Increase heart rate	Glycopyrrolate does not cross BBB or the placenta
	Can increase myocardial work and oxygen consumption	
Opioids	Complete reversal with naloxone	Morphine 0.2 to 2 IM, SC
	Analgesic	CRI 0.1 to 0.3 loading dose, then 0.1 mg/kg/hr
	Respiratory depression	Oxymorphone 0.05 to 0.2 IM, IV, SC
	Bradycardia	Meperidine 2 to 11 IM, SC
	Minimal effect on CV performance	Hydromorphone 0.1 to 0.2 IV, IM, SC
		CRI 0.025 to 0.05 IV loading dose, then 0.01 to 0.04 mg/kg/hr
		Fentanyl 0.005 to 0.08 IM, IV, SC
		CRI loading dose for dog 5 to 10 μg/kg, then 0.7 to 1 μg/kg/min
		CRI loading for cat 5 μg/kg, then 0.3 to 0.4 μg/kg/min
		Give anticholinergic drug before starting CRI
	Partial μ-agonist	Buprenorphine 0.005 to 0.02 IM, IV
	Partial reversal of μ-agonist with butorphanol	Butorphanol 0.1 to 0.8 IM, IV, SC CRI 0.1 to 0.2 IV loading dose, then 0.1 to 0.2 mg/kg/hr
	Complete reversal with naloxone	Naloxone 0.002 to 0.02 IM, IV
Dissociative agents	Salivation	Ketamine 4 to 11 IV, IM
		CRI 0.5 IV loading dose, then 0.1 mg/kg/hr
	Increase heart rate	Tiletamine and zolazepam (Telazol) 2 to 4 IM, 2 IV
	Increase ICP and intraocular pressure	
	Do have analgesic effects	
	Renal elimination in cat	

Benzodiazepines	Can decrease other drug dosages	Diazepam 0.2 to 0.5 IM, IV CRI 0.1 to 0.5 mg/kg/hr
	Mild sedation and muscle relaxation	Midazolam 0.07 to 0.4 IM, IV CRI 0.1 to 0.5 mg/kg/hr
	Anticonvusant	
	Not analgesic	
	Diazepam has propylene glycol	
Phenothiazines	Vasodilation	Acepromazine 0.01 to 0.2 IM, IV
		No more than 3 mg total dose
	Long duration	
	Not analgesic	
Barbiturates	Cardiovascular depression	Thiopental 4 to 20 IV
	Respiratory depression	Methohexital 4 to 10 IV
	Rapid induction	
	Decrease ICP and intraocular pressure	
	Effects may be potentiated by concurrent acidosis or hypoproteinemia	
	Can use with lidocaine	Lidocaine 2 to 4 IV with thiopental 4 to 8 IV
Propofol	Rapid acting with short duration	2 to 8 IV
		CRI 0.1 to 0.4 mg/kg/min
	Respiratory depression	
	Decreases ICP and intraocular pressure	
	Not analgesic	
	Caution with volume depletion or cardiovascular compromise; can be significant depression	
	Peripheral vasodilation	
	Myocardial depressant	
	Heinz body anemia in cats	
Etomidate	Maintain cardiovascular stability	0.5 to 4 IV
	Not used alone	
	Suppresses adrenocortical function for 2 to 6 hours following a single bolus dose	

α_2-Agonists	Cardiovascular depression	Xylazine 0.55 IM, IV
	Vomiting	Medetomidine 10 to 80 μg/kg IM, IV
	Good sedation and analgesia	CRI 1 μg/kg IV loading dose, then 1 to 3 μg/kg/hr
		Can combine with butorphanol or ketamine
	Reversible with atipamezole	Atipamezole 0.04 to 0.3 IM, IV
Neuroleptanalgesic	Analgesic	Combination of opioid and tranquilizer
	Noise sensitive	
	Maintain cardiovascular stability	
Inhalants	All inhalants will produce a dose-dependent cardiovascular depression and peripheral vasodilation	—
	Anesthesia depth adjusted rapidly	
	Isoflurane: Rapid uptake and recovery	
	Nitrous oxide: Caution with closed gas spaces	
	Potential for hypoxemia	
	Sevoflurane: Rapid uptake and recovery	

BBB, Blood-brain barrier; *CRI,* constant rate infusion; *CV,* cardiovascular; *ICP,* intracranial pressure; *IM,* intramuscular; *IV,* intravenous; *SC,* subcutaneous.

Maintenance requires careful and constant monitoring to avoid excessive anesthetic depth and to preserve cardiovascular function. The ECG should be monitored closely for changes in heart rate, rhythm, and for the presence of malignant arrhythmias, which may be more prevalent with trauma, splenic disease, septic peritonitis, hypoxia, or gastric dilatation-volvulus.

Additional monitoring during the maintenance phase includes maintaining the mean arterial blood pressure (MAP) higher than 60 mm Hg to maintain renal perfusion. Physical indicators of perfusion, such as the capillary refill time (CRT), mucous membrane color, and pulse quality, should be monitored continuously. Depth of anesthesia should be assessed frequently by monitoring eye position, pupil size, jaw tone, response to stimulus, heart rate, blood pressure, and respiratory rate.

Other monitoring techniques should be implemented, both during and post anesthesia, to enhance the quality of care and increase survival. Pulse oximetry will add information on hemoglobin (Hb) saturation and oxygenation.[12] It is important to remember that patients on inspired oxygen (FIO_2) of 100% may have a normal pulse oximetry reading but still have significant oxygenation abnormalities. For example, if a patient is place on an FIO_2 of 100, expected arterial partial pressure of oxygenation (PaO_2) should be 500 mm Hg if it has normal lung function. Hb is fully saturated (SpO_2 is 100%) once PaO_2 is greater than 110 mm Hg. Consequently when a pulse oximeter reads 100% on a patient breathing 100% oxygen, the PaO_2 can be anything from 110 to 500 mm Hg. This makes pulse oximetry a very insensitive measure of oxygenation.

Conversely an accurate pulse oximeter reading of anything less than 100% in a patient breathing 100% oxygen indicates a severe problem with the ability to oxygenate and should be treated as an emergency. Based on this, arterial blood gas monitoring may be necessary as the gold standard in those critically ill anesthetized patients. Arterial blood gas values will provide oxygenation, ventilation, Hb saturation, acid-base, and electrolyte information.

Capnography allows monitoring of the adequacy of ventilatory function and provides an indication of cardiac output (CO).[12] Capnography will also monitor for signs of esophageal intubation, breathing circuit disconnection, and cardiac arrest, where it will read zero carbon dioxide (CO_2).[12]

UOP should be monitored carefully, and a normal range of 1 to 2 ml/kg/hr should be achieved.[5] One can consider using an indwelling urinary catheter for precise measurement in patients with renal impairment or inadequate blood volume (where one would see decreased UOP).

Fluid overload can be assessed by measuring the body weight both preoperatively and postoperatively. Central venous pressure (CVP) measurement will help guide fluid therapy (normal 0 to 10 cm H_2O) and volume overload, but reflects only the right side of the heart.[5] In addition, CVP monitoring may not be accurate during IPPV as a result of changes in thoracic pressure.

Colloid osmotic pressure should be monitored frequently, as mentioned previously, to help determine the oncotic status of the patient and aid in fluid therapy choices. Blood glucose levels should be monitored closely in animals that are pediatric, septic, diabetic, or have severe liver disease. Finally, body temperature should be monitored continuously, because anesthetic drugs disrupt normal thermoregulatory mechanisms, and hypothermia leads to prolonged recovery.[13]

163.7 INTRAOPERATIVE HYPOTENSION

Because critically ill patients are often hypotensive during anesthesia, a mean blood pressure lower than 60 mm Hg 708
or a systolic pressure lower than 90 mm Hg requires prompt treatment to maintain adequate organ perfusion.[14] The 709
initial step should be to decrease the administration of inhalant anesthetic agents because of their depressant and vasodilatory properties. Next, a fluid bolus should be initiated. Either a crystalloid, without potassium supplementation in the fluids, at a rate of 10 to 20 ml/kg IV over 15 to 20 minutes or a colloid bolus of 5 to 10 ml/kg IV over 10 to 20 minutes should be given. If there is no effect, multiple small boluses can be attempted, keeping in mind the total volume of fluids that have been given.

If hypotension persists despite fluid therapy, there may be a need for vasopressor and/or inotropic support in the form of dopamine or dobutamine. These agents are given as a CRI because of their short half-lives, 2 to 10 µg/kg/min IV.[14] Dopamine and dobutamine can be used concurrently. Patients receiving inotropic medications and vasopressors should be monitored carefully for tachycardia, which may necessitate decreasing the rate of the infusion or the addition of another vasopressor. Other agents that may be used include ephedrine (0.05 to 0.5 mg/kg IV as a single bolus), norepinephrine (0.1 to 1 µg/kg/min IV as a CRI), and vasopressin (0.01 to 0.04 U/kg/hr IV as a CRI).[14,15]

If the initial vasopressor and/or inotrope does not correct the hypotension, a second agent is added while continuing administration of the first agent. For example, norepinephrine is used most often in combination with dopamine or dobutamine, and vasopressin can be used in combination with these agents as well.

If the animal continues to remain hypotensive even following appropriate fluid therapy and inotropic support, it may be necessary to consider discontinuing the inhalant anesthetic agent to eliminate its hypotensive effects and continuing anesthetic maintenance with injectable drug therapy. This may consist of a CRI of a μ-agonist such as fentanyl or morphine, in combination with ketamine and lidocaine. Some patients may need only fentanyl as an intermittent IV bolus or as a CRI. Research suggests a lidocaine CRI should not be used in the anesthetized cat because of the cardiovascular depressant effects it produces.[16]

163.8 RECOVERY

In these critically ill patients, continuous cardiovascular support, monitoring, supportive care, and analgesia are imperative during the recovery period. The recovering patient may still require vasopressor support, which should be continued in the intensive care unit.

The patient should be kept dry and warm, and should recover in a quiet, stress-free place where it can be continuously and carefully monitored. A shivering animal has greatly increased demands for glucose and oxygen, and oxygen supplementation and heat support should be given until the animal is no longer shivering.[7]

Acid-base status, electrolyte values, and blood glucose levels should also be monitored in the recovering and shivering animal. Forced warm air heating blankets will help to treat hypothermia.

Finally, analgesics are imperative in these painful, critically ill patients. Although these patients may not exhibit classic pain responses because of their debilitated states, they should be carefully and appropriately treated with analgesics. Pain can lead to catabolism and complications such as delayed wound healing, sepsis, and nosocomial disease[17] (see Chapter 164, Analgesia and Constant Rate Infusions).

163.9 CONCLUSION

Critically ill patients that need to be anesthetized should be stabilized aggressively before anesthesia. Appropriate monitoring should be performed at all times to ensure that these delicate patients survive emergency surgery. Postoperative care includes continued vasopressor and inotropic support, aggressive colloid and/or crystalloid therapy, analgesia, antibiotics, oxygen, blood pressure monitoring, and nursing care to improve survival in this critically ill population.

163.10 SUGGESTED FURTHER READING*

BH Cassutto, RW Gfeller: Use of intravenous lidocaine to prevent reperfusion injury and subsequent multiple organ dysfunction syndrome. *J Vet Emerg Crit Care*. **13**, 2003, 137, *An excellent review of lidocaine and its actions*.

EM Mazzaferro, E Rudloff, R Kirby: The role of albumin replacement in the critically ill veterinary patient. *J Vet Emerg Crit Care*. **12**, 2002, 113, *An excellent review of the role of albumin in the body*.

BH Pypendop, JE Ilkiw: Assessment of the hemodynamic effects of lidocaine administered IV in isoflurane anesthetized cats. *Am J Vet Res*. **66**, 2005, 661, *A well-done research paper on the use of lidocaine in the anesthetized cat and its potential deleterious effects on the cardiovascular system*.

B Wright, PW Hellyer: Respiratory monitoring during anesthesia: pulse oximetry and capnography. *Comp Cont Educ Pract Vet*. **18**, 1996, 1083, *A well-written review on pulse oximetry and capnography*.

* See the CD-ROM for a complete list of references

164 Chapter 164 Analgesia and Constant Rate Infusions

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164.1 KEY POINTS

- Analgesia can be achieved with several general drug classes, administration routes, and techniques.
- Develop an analgesic therapeutic plan that assesses the type and severity of pain.
- Patients should be evaluated frequently for response to treatment and given additional analgesics if necessary.
- Multimodal or combination analgesic drug therapy may be beneficial in the critically ill patient.

164.2 ANALGESIA

The critical care patient will benefit from analgesia, because it promotes an animal's overall well-being and has a positive effect on the speed and quality of recovery.[1] The goal of pain control is to achieve a state whereby the pain is bearable and some of its protective aspects, such as inhibiting use of a fractured leg, remain.[1] There are several general drug classes, administration routes, and techniques by which analgesia can be achieved. General drug classes that commonly are used include the following: opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), α_2-adrenergic agonists, local anesthetics, N-methyl-D-aspartate (NMDA) antagonists, benzodiazepines, and phenothiazines. Analgesia can be administered via intravenous, subcutaneous, intramuscular, epidural, transmucosal, transdermal, local infiltration, oral, intraarticular, intrapleural, and intraperitoneal routes. The type of treatment may depend on the severity of pain and the nature of the animal.

In critically ill patients, analgesics should be administered as soon as possible following assessment to provide a significant benefit.[2] It is vital, however, that the underlying disease process be addressed before pain relief is provided, because analgesia may mask the underlying disease processes or the hemodynamic stability of a patient. Ideally, analgesics can be administered before pain develops (e.g., preemptive analgesia), because less drug therapy may be necessary to control pain. This is especially important before surgery or other invasive procedures; however this is not always feasible in trauma cases or in emergency cases.[2,3]

Pain development and sensation may involve a multiplicity of pathways; therefore it is important to develop a therapeutic plan that assesses the type and severity of the pain and the response to treatment. Because pain pathways are complex, it is often unlikely that one agent alone will completely alleviate pain, regardless of how high the dosage is.[4] Use of drugs from more than one class can improve analgesia by targeting multiple receptor types and may also overcome the problem of varying onset times and durations. Examples of effective combinations include using opioids with NSAIDs, local anesthetics (e.g., Lidoderm patches) with opioids, or using epidural analgesia with systemic opioid therapy. Regardless of what type of analgesia or combination of agents is used, patients should be reassessed frequently to ensure that the regimen is adequate and appropriate. Finally, analgesics may be diagnostic when pain behavior is difficult to recognize in stoic patients.[4]

164.2.1 Opioids

Opioids act centrally to limit the input of nociceptive information to the central nervous system (CNS), which will reduce central hypersensitivity.[5] Receptors in the brain and dorsal horn of the spinal cord receive impulses from peripheral nerves, which are modulated before being transmitted to higher centers.[6] Opioids commonly are used in critically ill patients because they have a rapid onset of action and are safe, reversible, and potent.[7] As with all analgesic therapy in critically ill patients, opioids should be slowly titrated IV to effect, because drug pharmacokinetics may be altered.[7] Opioid analgesics vary in effectiveness, depending on which receptor is stimulated and which class of opioid is being administered.

The four classes of opioids are pure agonists, partial agonists, agonist-antagonists, and antagonists. Pure receptor agonist stimulation results in a pronounced analgesic effect, and partial agonists bind at the same receptor but produce a less pronounced effect.[6] Agonist-antagonists have mixed effects, with an agonist effect at one type of receptor and an antagonist effect at a different type of receptor. This results in an analgesic effect at one receptor and no effect (or a less pronounced effect) at the other receptor. Opioid antagonists (e.g., naloxone) bind to the same receptor as agonists but cause no effect, and can competitively displace the agonist from the receptor and therefore reverse the agonist effect.[6] Partial agonists (e.g., buprenorphine 5 to 20 μg/kg IV, IM, or SC q6-8h) and mixed agonist-antagonists (e.g., butorphanol 0.1 to 0.4 mg/kg IV q1-4h) reach maximal effect at the upper end of the dosage range (see Table 164-1 for further information on appropriate dosing, routes of administration, and intervals).[5] If the pain is severe or the analgesia is inadequate, additional doses of partial or mixed agonist-antagonists are unlikely to be effective.[5] Using a pure μ-agonist (e.g., morphine, hydromorphone, fentanyl, oxymorphone) would be more effective, because there is no upper limit to the analgesia provided by these agents.[5]

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Table 164-1 Analgesic Agents and Their Dosages

Generic	Range in Dosage	Brand, Manufacturer
Acetylpromazine, acepromazine	0.01 to 0.05 mg/kg IM, IV, SC q3-6h Do not exceed a total of 2 mg in large dogs	Aceproject, Fort Dodge
Atipamezole	0.05 to 0.2 mg/kg IM, SC, IV Reversing α_2-adrenergic agonist	Antisedan, Pfizer
Bupivacaine	*Nerve block:* 1 to 2 mg/kg SC q6h *Epidural* *Dog:* 0.6 to 2 mg/kg *Cat:* 0.5 to 1 mg/kg	Abbott Laboratories
Buprenorphine	5 to 20 µg/kg IM, IV q6-8h *Cat:* 10 to 20 µg/kg PO q6-8h *Epidural:* 3 to 6 µg/kg	Buprenex, Reckitt & Colman
Butorphanol	0.1 to 0.4 mg/kg IM, IV q1-4h *Partial reversal of µ-opioid agonist:* 0.05 to 0.1 mg/kg IV *Loading dose for CRI:* 0.1 mg/kg IV *Maintenance for CRI:* 0.1 to 0.4 mg/kg/hr IV	Torbutrol, Torbugesic-SA, Fort Dodge
Carprofen	2 to 4 mg/kg SC (single dose)	Rimadyl, Pfizer
Deracoxib	*Dog:* 1 to 2 mg/kg PO q24h *Postoperative pain:* 3 to 4 mg/kg PO q24h, not given for more than 7 days	Deramaxx, Novartis
Etodolac	*Dog:* 5 to 15 mg/kg PO q24h	EtoGesic, Fort Dodge
Fentanyl	*Loading dose in dogs:* 2 µg/kg IV *Maintenance in dogs:* 2 to 5 µg/kg/hr CRI *Loading dose in cats:* 1 µg/kg IV *Maintenance in cats:* 1 to 2 µg/kg/hr CRI *Anesthetic dose in cats:* 0.1 to 0.4 µg/kg/min CRI	Abbott Laboratories
Fentanyl patch	*Cat or dog under 5 kg:* 25-µg patch *Dog 5 to 10 kg:* 25-µg patch *Dog 10 to 20 kg:* 50-µg patch *Dog 20 to 30 kg:* 75-µg patch *Dog over 30 kg:* 100-µg patch	Duragesic, Janssen Pharmaceuticals

Hydromorphone HCl	*Dog:* 0.05 to 0.2 mg/kg IM, SC; 0.05 to 0.1 mg/kg IV q4-6h *Cat:* 0.05 to 0.1 mg/kg IM, SC q3-4h; 0.03 to 0.05 mg/kg IV q3-4h	Baxter Healthcare
Ketamine	*Analgesia without sedation:* 0.1 to 1 mg/kg IV *Loading dose:* 0.5 mg/kg IV *Maintenance during surgery:* 10 µg/kg/min CRI IV *Maintenance after surgery:* 2 µg/kg/min CRI for 24 hr	KetaFlo, Abbott Laboratories Ketaset, Fort Dodge Animal Health Vetalar, Bioniche Animal Health Vetamine, Schering-Plough
Lidocaine 1% Dog only	*Nerve block:* 1 to 2 mg/kg SC *Loading dose:* 1 to 2 mg/kg IV *Maintenance:* 25 to 80 µg/kg/min; up to 2 to 3 mg/kg/hr CRI IV	1% Preservative free, Abbott Laboratories
Lidocaine 2%	*Nerve blocks:* 1 to 2 mg/kg SC	Phoenix Pharmaceuticals
Lidocaine patch	No animal dosage established, but patch is 700 mg of lidocaine. Significant systemic absorption has not been found. Patch should be cut to fit size of area.	Lidoderm (5% lidocaine patch), Endo Pharmaceuticals
Medetomidine	1 to 10 µg/kg IV q4h *Loading dose:* 1 µg/kg IV *Maintenance:* 1 to 3 µg/kg/hr IV CRI	Domitor, Pfizer
Meloxicam	0.1 to 0.2 mg/kg IV, SC (single dose)	Metacam, Boehringer Ingelheim
Morphine (preservative free)	*Dog:* 0.25 to 1 mg/kg IM q4-6h *Epidural:* 0.1 to 0.4 mg/kg *Cat:* 0.05 to 0.5 mg/kg IM *Epidural:* 0.16 mg/kg *Dogs and cats epidural:* 0.3 mg/kg q24h as slow infusion *IV CRI:* Loading dose: 0.15 to 0.5 mg/kg slow IV to avoid histamine release *IV CRI Maintenance:* 0.1 to 1 mg/kg/hr IV	Infumorph, Baxter Healthcare; Astramorph, PF Astra
Morphine sulfate with preservative	*Dog:* 0.5 to 2 mg/kg IM, SC q4h *Cat:* 0.05 to 0.4 mg/kg IM, SC q3-6h	Baxter Healthcare
Naloxone	0.002 to 0.1 mg/kg IM, IV, SC	Narcan, DuPont Pharm

Oxymorphone	*Dog:* 0.03 to 0.1 mg/kg IM, IV *Cat:* 0.01 to 0.05 mg/kg IM, IV	Numorphan, Endo Labs
Tepoxalin	*Dog:* 10 mg/kg PO q24	Zubrin, Schering-Plough Animal Health
Morphine-lidocaine-ketamine infusion	*Morphine:* 3.3 μg/kg/min *Lidocaine:* 50 μg/kg/min *Ketamine:* 10 μg/kg/min *Preparation:* Mix 10 mg of morphine sulfate, 150 mg of 2% lidocaine, and 30 mg of ketamine into a 500-ml bag of lactated Ringer's solution *Administration:* 10 ml/kg/hr	—

CRI, Constant rate infusion; *IM,* intramuscular; *IV,* intravenous; *PO,* per os; *SC,* subcutaneous.

Potent side effects such as respiratory depression and bradycardia may be seen at the higher dosage range with a pure μ-agonist; therefore, the higher dosage range should be used cautiously in critically ill patients.[5,6] Additional side effects of μ-agonists (e.g., morphine and meperidine) include histamine release, particularly when given rapidly intravenously, which can lead to severe hypotension due to vasodilation.[6] Opioids can create gastroparesis and ileus, which may result in vomition, regurgitation, and aspiration of gastrointestinal (GI) contents, particularly in depressed, sedated, weak, or critically ill patients.[8] Gastric distention from opioids may also be a concern in patients with abdominal disease (e.g., pancreatitis), because stimulation of pancreatic secretions may occur.[8] Patients at risk for pancreatitis or gastroparesis may require intermittent or constant gastric decompression (via nasogastric or gastrostomy tube) if they are treated with opioids for more than 12 to 24 hours, or they may require motility drug therapy (e.g., metoclopramide).[8]

In cats, opioids can be administered safely to provide analgesia.[5] Morphine (0.05 to 0.5 mg/kg IM q3-6h) or oxymorphone (0.05 mg/kg IV titrated slowly) can be given for analgesia; however, side effects such as hyperexcitability or agitation may occur. It has been shown that the onset of mydriasis following administration of opioids correlates with adequate analgesia in cats; continued administration after achieving mydriasis may result in adverse side effects such as dysphoria and agitation.[8] The mixed partial μ-agonist buprenorphine (10 to 20 μg/kg PO q6-8h) is an effective analgesic in cats and can also be used.[6]

One advantage of opioid administration in critically ill patients is that their effects can be reversed, if necessary, with a pure antagonist such as naloxone (0.002 to 0.1 mg/kg IV, IM, or SC). Naloxone can reverse CNS depression, respiratory depression, and bradycardia, but the reversal of sedation and analgesia can cause pain, excitement, emergence delirium, aggression, and hyperalgesia.[9] Low-dose naloxone (0.004 mg/kg IV titrated slowly) has been recommended to reverse CNS depression without affecting analgesia.[8] The duration of effect for naloxone is relatively short (20 to 30 minutes) because of its rapid metabolism in dogs and cats, which may predispose patients to renarcotization when the drug is used to reverse long-acting opioids.[9,10]

Agonist-antagonists such as butorphanol (0.05 to 0.1 mg/kg IV) may also be used to reverse sedation and respiratory depression from μ-agonists.[8,9] The benefit of using butorphanol as a reversal agent is that complete reversal of analgesia does not occur because of its κ-agonist effects. Use of butorphanol as a reversal agent may produce additive analgesia with the μ-agonist.[9] In contrast, buprenorphine is not as easily reversed as butorphanol, because it is difficult to displace from the receptor.[6]

164.2.2 Nonsteroidal Antiinflammatory Drugs

Inflammation plays a significant role in the pain process; thus, reducing or eliminating peripheral inflammation with NSAIDs may be helpful. NSAIDs decrease the pain input to the CNS, which may aggravate central hypersensitivity.[2] There are several commercially available NSAIDs, including carprofen, deracoxib, meloxicam, etodolac, and tepoxalin. The analgesic and antiinflammatory effects associated with NSAID administration are related to inhibition of cyclooxygenase (COX) enzyme isoforms.[11] COX-1 is responsible for basal prostaglandin production for normal homeostatic processes within the body, including gastric mucus production, platelet function and, indirectly, hemostasis, and COX-2 is found at sites of inflammation.[11] Ideally, selective inhibition of prostaglandins produced primarily by COX-2 would allow analgesic and antiinflammatory effects without the unwanted side effects from COX-1 inhibition.[11] At present, there is no pure COX-2 inhibitor; rather, certain NSAIDs may have varying degrees of COX-1 inhibition. For this reason, NSAIDs should be used cautiously in cats, or in canine patients with hypotension, hypovolemia, preexisting renal disease, or GI disease because of the increased potential for renal vascular vasoconstriction (resulting in worsening renal insufficiency) and gastric ulceration.[5,7,12] Due to the clinical incidence of acute renal failure after NSAID administration in cats, the use of NSAIDS is only recommended in healthy, euvolemic, hydrated feline patients.

Ideally, enteral NSAIDs should be given with food when possible to decrease the incidence of gastric ulceration. In addition, NSAIDs should be used cautiously during the perioperative period, because decreased platelet function may increase the incidence of operative hemorrhage. For canine patients, injectable NSAIDs (e.g., carprofen 2 to 4 mg/kg IV or SC, meloxicam 0.1 to 0.2 mg/kg IV or SC) have an advantage over oral NSAIDs, because injectable drug therapy can be used in patients that cannot tolerate oral administration because of preoperative fasting for anesthesia, nausea, vomiting, or decreased mentation.[5] Finally, although NSAIDs have a slow onset of action (taking up to 45 to 60 minutes to take effect), they provide analgesia for an extended period.[13] Carprofen has a 12-hour dosing frequency, whereas other NSAIDs (e.g., deracoxib, meloxicam, etodolac) are labeled for once-daily dosing.[11] As mentioned previously, NSAIDs can be used in combination with opioids for a combined therapeutic effect in the stable patient.[5] Glucocorticoids and NSAIDs should not be used concurrently because of the potentiated GI side effects of COX-1 inhibition.[5]

164.3 α_2-ADRENERGIC AGONISTS

α_2-Adrenergic agonists bind to receptors in the CNS, leading to sedation, peripheral vasoconstriction, bradycardia, respiratory depression, diuresis, muscle relaxation, and analgesia.[8,14] Medetomidine is the most common α_2-adrenergic agonist administered in small animals. Sedative effects of medetomidine have a longer duration of action than do the analgesic effects, which last approximately 30 to 90 minutes.[15] Low-dose medetomidine (1 to 10 μg/kg IV) can be used safely in stable patients, or administered in conjunction with opioids to produce analgesic synergism and increase the analgesic duration to as long as 4 hours.[8,15] At higher dosages, medetomidine can be used to sedate distressed animals and for minor procedures (e.g., restraint and analgesia for radiographic positioning).[8] In the cardiovascularly stable patient, medetomidine can be used as a constant rate infusion (CRI) for analgesia (loading dose is 1 μg/kg IV then CRI of 1 to 3 μg/kg/hr).[16] As with opioids, the effects of α_2-adrenergic agonists can be reversed. Atipamezole (0.05 to 0.2 mg/kg IM, SC, or IV) is a specific α_2-adrenergic antagonist that reverses analgesia, sedation, and respiratory depression, and is the same volume as the amount used of medotomidine.[9] Intramuscular or subcutaneous routes of administration are preferred for reversal, because intravenous administration can lead to abrupt hypotension and/or aggression.[9]

164.4 TRANSDERMAL ANALGESIA

Administering topical analgesia in conjunction with existing analgesic therapy is well tolerated by patients and has minimal systemic effects.[17] Fentanyl patches (Duragesic) can be used to provide long-term analgesia but may vary in time of onset and steady-state concentrations.[7,13,18] Because of this variability, systemic analgesia must be provided until the patch becomes effective. Fentanyl uptake depends on dermal blood flow, hair, and obesity and may be greatly altered in hypovolemic or hypothermic patients. In dogs, it may take up to 24 hours to reach effectiveness.[8] Cats may reach therapeutic levels in 6 to 12 hours and can maintain steady states for approximately 5 days.[13,18]

It should be noted that not all animals reach therapeutic levels with the patch. If patients still appear to be in pain 12 to 24 hours after patch placement, additional treatment with analgesics may be necessary.[8] Fentanyl is available in 25-, 75-, and 100-μg patches. If a lower dose is desired, part of the seal can be retained to prevent absorption.[13] Fentanyl patches should not be cut or otherwise altered, because this may affect the amount of absorption or result in drug loss. Disposal of fentanyl patches should be appropriately directed, because there is potential for human abuse.

Lidoderm, a 5% lidocaine patch, has been introduced to the human and veterinary markets. Lidoderm was approved in 1999 by the U.S. Food and Drug Administration for treatment of postherpetic neuralgia in humans.[17] Lidoderm is a nonwoven, polyester, felt-backed patch covered with a polyethylene terephthalate film release liner that should be removed before applying it to skin. Each 10- × 14-cm adhesive patch contains 700 mg of lidocaine and 50 mg/g adhesive in an aqueous base. Lidocaine penetration into intact skin is sufficient to produce an analgesic effect but does not result in complete sensory block. The Lidoderm patch can be safely worn for as long as 24 hours and provides analgesia without numbness or loss of sensitivity to touch or temperature.[19] Therapeutic levels are achieved via absorption within 30 minutes, and toxic blood levels have not been documented.[19]

Unlike the fentanyl patch, the Lidoderm patch can be cut to fit the patient without affecting drug delivery.[19] Lidocaine patches can be used in a back-to-back continuous fashion, because toxic blood levels do not develop. The skin should be monitored for localized dermatitis, as the most common adverse effect in humans is transient dermal reactions (such as a localized rash and pruritus).[19]

For veterinary use, the hair must be clipped and cleaned. The patch can be anchored with surgical staples to ensure appropriate contact with skin.[20] Anecdotally, the Lidoderm patch has been used in dogs and cats to provide analgesia for severe skin abrasions, severe bruising, and surgical incisions; no apparent toxic effects have been noted. In addition, multimodal analgesia can be initiated with both the lidocaine and fentanyl patches applied simultaneously. Lidoderm will provide local analgesia, and the fentanyl patch will provide systemic analgesia.

164.5 N-METHYL-D-ASPARTATE ANTAGONISTS

NMDA receptor antagonists work when blockade of multiple binding sites results in analgesic, amnestic, psychomimetic, and neuroprotective effects.[21] Ketamine can reverse central hypersensitivity by preventing the exaggerated response, wind-up activity, and central sensitization of wide–dynamic range neurons in the dorsal horn of the spinal cord.[5] Ketamine, a noncompetitive NMDA receptor antagonist, can be administered orally, subcutaneously, intramuscularly, and intravenously. It prevents the response to nociceptive stimuli carried by afferent pain neurons (e.g., C fibers).[22,23] Ketamine causes minimal cardiovascular depression, does not depress laryngeal protective reflexes, and produces less ventilatory depression than do opioids; however, side effects include tremors and sedative effects, along with increased cardiac output via increased sympathetic tone.[23] Subanesthetic or low doses in dogs and cats (0.1 to 1 mg/kg IV, followed by a CRI at 2 to 10 μg/kg/min), may produce analgesic effects without causing anesthesia or profound sedation.[5,23] Oral ketamine can also be used (dogs: 8 to 12 mg/kg PO q6h) to provide pain relief following burn injuries.[7]

164.6 ACETYLPROMAZINE

Acetylpromazine (0.01 to 0.05 mg/kg IV, not to exceed a total of 2 mg) may be used in combination with opioids as an anxiolytic and sedative.[8] Acetylpromazine should be used with caution because of the potential for vasodilation and resultant profound hypotension and hypothermia.[8] Acetylpromazine does not provide analgesia and should not be administered as a single agent if analgesia is desired.[8] It may take up to 15 minutes before the sedative effect of an intravenous dose of acetylpromazine is clinically observed; therefore further doses should not be given until the full effect is evident.[8] Acetylpromazine can be administered safely to intensive care patients if given at ultra-low doses (0.005 to 0.01 mg/kg) in hemodynamically stable animals with adequate respiratory function.[24]

164.7 INFILTRATIVE AND LOCAL ANESTHETICS

Local anesthetics (e.g., lidocaine, bupivacaine) provide analgesia by blocking both specific nerve pathways and action potential transmission in nerve fibers (including nociceptive fibers).[5] They can be used for local injection (e.g., small bite wounds on the muzzle), intercostal nerve blocks (e.g., rib fractures), and intrathoracic or intraperitoneal administration. In addition, 0.5% bupivacaine (2 mg/kg q6h) can be administered for painful diseases and conditions (e.g., fractures, pancreatitis) or procedures (e.g., thoracotomy, thoracostomy tube placement).[5,13] Intercostal nerve blocks can be performed to provide analgesia for rib fractures. Bupivacaine (1 to 1.5 mg/kg q6h; not to exceed 4 mg/kg on day 1) can be injected in the area of the intervertebral foramen on the caudal border of the rib to block the intercostal nerves.[5] Bupivacaine can also be administered intrapleurally via a thoracostomy tube to provide analgesia following thoracic surgery or tube placement, because the presence of the tube itself may be painful. In cases of pancreatitis or abdominal pain, bupivacaine can be administered intraperitoneally (2 mg/kg q6h diluted in saline) with an aseptically placed, temporary butterfly catheter to provide analgesia. However, this may be ineffective when ascites is present, due to a dilutional effect.

When using local anesthetics, aseptic technique is imperative. The patient should be positioned so that the medication disperses over the desired site to enhance analgesia.[5] In addition, sodium bicarbonate (1 mEq/ml) may be added to lidocaine (at a ratio of 1 to 2 parts bicarbonate to 8 to 9 parts lidocaine) to decrease the burning sensation caused by lidocaine alone; this effect is caused by the acidity of the local anesthetic.[8] When using bupivacaine, a 1:30 ratio of sodium bicarbonate to bupivacaine is sufficient.

Side effects of bupivacaine include arrhythmias and reduced cardiac output; therefore the drug should not be administered in animals with preexisting, life-threatening arrhythmias.[8] Also, because bupivacaine is selectively cardiotoxic, only half of the canine dose should be given to cats.[8] Certain contraindications for bupivacaine warrant the use of alternative analgesics. In patients undergoing a pericardectomy, bupivacaine should not be administered intrapleurally because the risk of cardiotoxicity.[5] Intrapleural bupivacaine may also interfere with ventilation by inducing diaphragmatic paralysis.[8] Animals with good respiratory reserve capacity rarely develop clinically significant compromise, but administration of intrapleural anesthetics should be avoided in animals with marginal respiratory function.[8]

Finally, toxicity may occur with higher doses of lidocaine (>10 to 20 mg/kg) and bupivacaine (>4 mg/kg).[5] Clinical signs of toxicosis may include seizures, cardiac arrhythmias, tachycardia, and cardiovascular collapse. The maximum safe dosage for most species is 4 mg/kg of lidocaine and 1 to 2 mg/kg of bupivacaine.[5] Epinephrine, which normally enhances the duration of effect of local anesthetics, should be avoided in critically ill patients, as it may lead to cardiac stimulation or ischemia from vasoconstriction.[5]

164.8

EPIDURAL ANALGESIA

Epidural analgesia is an alternative way to deliver analgesia to the caudal half of the body.[5] Depending on the dosage or volume used, analgesia of the forelimbs can also be achieved, because 1 ml/5 kg blocks to the first lumbar vertebra using the larger volume results in cranial spread of the analgesic.[5] Lower concentrations of local anesthetics can provide analgesia without secondary motor deficits.[5] Complete anesthesia can be achieved with higher doses of local anesthetics and result in temporary motor paralysis of the rear limbs.[5]

Epidural opioids can provide analgesia without affecting motor function; nociceptive input is reduced but not completely abolished.[5] Higher dosages may lead to vasodilation and subsequent hypotension.[5] In critically ill patients, lower dosages of local anesthetics should be used epidurally to prevent hypotension. Critically ill patients requiring general anesthesia often benefit from epidural analgesia, as it may decrease anesthesia requirements while providing analgesia without cardiorespiratory effects or hypotensive effects from inhalant therapy.

The technique for epidural analgesia has been described previously.[5] (Readers are referred to reference 5 for further information). Contraindications for epidural analgesia or epidural catheter placement include trauma over the pelvic region (with loss of appropriate landmarks), septicemia, coagulopathy, CNS disease, skin infection over the site of injection, hypovolemic shock, or severe obesity.[5,13,25,26]

Epidural catheters can be used to help maintain long-term analgesia, although stringent aseptic protocol must be followed. These catheters may be technically difficult to place. An epidural catheter can be placed using the same landmarks as those for a single injection. The advantage of epidural catheterization is that continuous analgesia can be provided without repeated punctures. In addition, the catheter can be advanced cranially to improve analgesia to the front limbs or thoracic structures. Catheters must be placed aseptically under anesthesia or heavy sedation and maintained with sterility and care. Proper epidural catheter placement can be confirmed with a lateral radiograph or fluoroscopy. If the catheter is not radiopaque, a low dose of myographic contrast agent can be injected into it in order to evaluate and ensure appropriate placement. Catheters have been left in place safely for 1 to 332 hours.[26] With epidural catheters, the total volume injected should be limited to 6 ml in a large dog.[26]

Morphine and bupivacaine are safe and effective epidural agents for dogs and cats.[25] Because of its lipid solubility and long duration of action, morphine is the opioid of choice for this purpose.[5] Morphine administered epidurally has a significantly longer duration of action than does a systemic dose.[25] Preservative-free solution should be used in the epidural space to ensure that there is no chemical damage to the spinal cord; this is especially important for intrathecal or spinal administration.[27] A one-time dose of preservative-free morphine diluted with sterile water or saline in the epidural space is not considered dangerous. The dosage of morphine in dogs ranges from 0.1 to 0.4 mg/kg, with a maximum volume of 6 ml.[25] The onset of action of morphine delivered epidurally is 20 to 60 minutes, with a duration of 6 to 24 hours.[5,27]

Bupivacaine can be administered at a dosage of 0.6 to 2 mg/kg (in dogs); however, the higher end of the range may result in transient paralysis.[25] The onset of action for bupivacaine can take up to 60 minutes, and the duration of action is similar to that of morphine.[5] Epidural buprenorphine may have some advantage over morphine, as urinary retention is less likely.[5,8,26,27]

For cats, morphine can be administered at 0.16 mg/kg and bupivacaine at 0.5 to 1 mg/kg; these doses provide epidural analgesia for approximately 20 hours.[25] In dogs, when using an epidural catheter, the following drugs and dosages can be administered as a slow bolus, providing analgesia for approximately 12 to 24 hours: morphine (0.1 mg/kg), bupivacaine (0.05 to 0.12 mg/kg), or buprenorphine (3 to 6 μg/kg).[26] Finally, when injecting an agent through the epidural catheter, the injection should be done slowly because a rapid injection may precipitate vomiting.

Side effects of epidural anesthesia include vomiting, urinary retention, pruritus, and delayed hair growth at the clipped epidural site.[25] Additional complications associated with epidural catheters include catheter dislodgement, discharge from the site, fecal contamination, line or filter breakage, and localized dermatitis.[28] When complications occur, removal of the epidural catheter is recommended.[28] Side effects should be treated symptomatically. Urinary retention can be treated or prevented by manually expressing the bladder or inserting an indwelling urinary catheter.

Vomiting is commonly associated with administering a loading dose of analgesia in conscious animals through the epidural catheter.[26] This may be a function of the volume and speed of injection rather than the type of agent administered.[26] Therefore all epidural drugs should be administered slowly.[26] A slow infusion of morphine (0.3 mg/kg q24h) or bupivacaine (0.2 to 0.3 mg/kg q24h) can be given into the epidural space using a syringe pump. While bupivacaine can be administered as a CRI, it may result in muscle weakness. If the weakness is excessive, the epidural infusion should be promptly discontinued and the dosage reduced.[26]

Another complication includes inadvertent subarachnoid space injection of drugs. In dogs, the dural sac ends before the lumbosacral space, so inadvertent injection of the subarachnoid space is less likely. In cats, however, the dural sac ends past the lumbosacral space; therefore care must be taken to avoid subarachnoid injection.[26] If the subarachnoid space is penetrated, a drug without preservatives may still be given; however, a significantly reduced dosage (i.e., 50% to 75% of the original dosage) should be administered.[26] The lower dosage is sufficient for an analgesic response because the roots of the spinal cord are more accessible within the subarachnoid space, where they are not protected by the dura.[29]

164.9 CONSTANT RATE INFUSION

Intravenous CRI of analgesics has the advantage of maintaining effective plasma concentrations for continued pain relief. All CRIs should be delivered by syringe pump for accurate dosing.[23] To avoid histamine release, which may occur with rapid IV morphine administration, a CRI (0.1 to 1 mg/kg/hr) should be started after giving a loading dose (0.15 to 0.5 mg/kg IV, diluted and given slowly over 5 to 10 minutes).[7,30] A CRI of morphine (0.12 mg/kg/hr) reportedly induces similar effects to intramuscular morphine (1 mg/kg q4h) in dogs undergoing laparotomy.[31] Regardless of how morphine is administered, its use may result in bradycardia, vomition, hypothermia, and panting.[31] Opioids other than morphine can be used if undesirable side effects occur. Butorphanol has been administered at a loading dose of 0.1 mg/kg followed by an infusion of 0.1 to 0.4 mg/kg/hr.[7] In dogs, lidocaine can also be used for pain control via CRI at an initial loading dose of 1 to 2 mg/kg followed by 25 to 80 µg /kg/min.[30] Lidocaine dosages as high as 2 to 3 mg/kg/hr IV have been reported.[12]

As previously discussed, ketamine given perioperatively may prevent “wind-up” pain from occurring and thereby reduce postoperative pain.[23] Low dosages of ketamine do not create the undesirable side effects such as dysphoria or hallucination and can be used for intraoperative and postoperative analgesia in dogs.[23] A loading dose of ketamine (0.5 mg/kg IV) should be followed immediately by a CRI of 10 µg/kg/min. This should then be reduced to 2 µg/kg/min during the recovery and postoperative phases.[23]

Fentanyl can be given to enhance analgesia, starting with a loading dose of 2 µg/kg IV, followed immediately by 2 µg/kg/hr IV.[23] This dosage can be increased as needed up to 5 µg/kg/hr IV.[23] In cats, fentanyl is also a safe analgesic when administered at a loading dose of 1 µg/kg IV followed by 1 to 2 µg/kg/hr; doses as high as 0.1 µg/kg/min IV as a CRI can be used, but this dose creates a plane of anesthesia and deep sedation.[18,32] In critically ill animals that are poor anesthetic candidates, fentanyl in conjunction with propofol can provide adequate, safe, cardiovascular-sparing anesthesia, therefore reducing or minimizing the amount of inhalant anesthetic necessary.[32] Side effects such as bradycardia may require treatment with an anticholinergic drug.[32]

164.10 MORPHINE-LIDOCAINE-KETAMINE

Morphine (3.3 µg/kg/min), lidocaine (50 µg/kg/min), and ketamine (10 µg/kg/min) can be administered as a CRI analgesic combination in dogs.[22] These agents can be given separately or mixed together in a single bag.[22] Using a combination of agents may result in enhanced analgesia through synergism and multiple receptor activation. Ketamine attenuates and reverses morphine tolerance in rodents and humans, thereby yielding an opioid-sparing effect and providing analgesia superior to that of either drug alone.[22] Work in the cat has shown that CRIs of lidocaine should be used cautiously, if at all, in this species because of cardiopulmonary depression; this would be an especially important consideration in the critically ill animal.[33]

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164.11 CONCLUSION

Administering analgesics to critically ill animals should be considered an integral part of a treatment regimen. These patients may present a challenge when clinicians assess them for pain and evaluate the response to analgesic therapy. Because of potential physiologic effects of some analgesics, the class of analgesic and route of administration should be chosen carefully. Multimodal therapy that emphasizes lower dosages of various classes of drugs may be a safer and more effective way of achieving analgesia in critically ill patients.

164.12 SUGGESTED FURTHER READING*

P Dobromylskyj, PA Flecknell, BD Lascelles, et al.: Management of postoperative and other acute pain. In P Flecknell, A Waterman-Pearson (Eds.): *Pain management in animals*. 2000, Saunders, Philadelphia, *An easily read text that details methods to achieve analgesia. Discusses pain and its treatment in a variety of species*.

B Hansen: Acute pain management. In KA Mathews (Ed.): *The Veterinary Clinics of North America Small Animal Practice: management of pain*. 2000, Saunders, Philadelphia, *A detailed discussion on various techniques that can be used to manage pain in small animals*.

BD Hansen: Epidural catheter analgesia in dogs and cats: Technique and review of 182 cases (1991-1999). *J Vet Emerg Crit Care*. **11**, 2001, 95, *A good overview of the use and technique of epidural catheters in small animals*.

KA Mathews: Management of pain in cats. In LJ Hellebrekers (Ed.): *Animal pain: a practice-oriented approach to an effective pain control in animals*. 2000, Van Der Wees, Utrecht, *A nice discussion on the particular differences in analgesic requirements of the feline patient.*

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* See the CD-ROM for a complete list of references

165 Chapter 165 Alternative Therapies

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165.1 KEY POINTS

- Veterinarians caring for critically ill patients may face a variety of requests from clients asking whether complementary medicine might benefit their animals while in the intensive care unit (ICU). Determining which therapies will benefit ICU patients can be challenging without species-specific evidential support.
- Delegating care to people who are not veterinarians or to people with questionable or unfamiliar credentials adds risk for animals and exposure for veterinarians already managing a busy caseload.[1] Practitioners trained to work with humans who are unfamiliar with zoonotic disease transmission and the fragile health status of critically ill animals may complicate the picture.
- Complementary therapies under consideration for ICU patients should be evaluated on a case-by-case basis. Even natural treatments that are indicated and safe for one patient may be contraindicated and potentially injurious to another.
- Acupuncture offers a versatile, adjunctive, analgesic approach for acute and chronic pain.[2] In addition, acupuncture's actions on autonomic regulatory pathways assist the body in recovering from surgery, trauma, and debilitating illnesses.
- Massage can relieve muscle pain and tension and can alleviate stress.[3-5]
- Physical therapy can be especially important for patients recovering from spinal cord injury and orthopedic or neurologic surgery.[6] On the other hand, aerobic exercise that places excessive demands on deconditioned patients may compromise cardiopulmonary and musculoskeletal function.[7]
- Herbs pose several hazards such as known and unknown drug-herb interactions, unclear dosing parameters, and questionable manufacturing practices and safety.
- Aromatherapy (essential oil therapy) may help calm certain animals, although subjecting staff and other patients to volatile substances known to be sleep-inducing, epileptogenic, or allergy-provoking may pose a workplace hazard or affect nearby patients in an untoward manner.
- High-velocity chiropractic adjustments and other forceful maneuvers may injure debilitated patients and should generally be avoided in ICU patients unless clearly indicated.
- “Glandulars,” unregulated products made from bovine or porcine glands or central nervous system components, may contain active hormones, contaminants, or diseased tissue, have no proven benefit, and pose obvious risk.

165.2 INTRODUCTION

Human intensive care unit (ICU) patients suffer from a variety of stressors, including fear, pain, anxiety, lack of sleep, loneliness, lack of control, nightmares and, for those on prolonged mechanical ventilation, inability to speak and perhaps communicate.[8] Severely ill animals likely find the experience similarly upsetting. According to one of the leading researchers in the ethics of human critical care, “Alleviating the stresses and symptoms of critically ill patients will enhance the quality of their ICU stay, which itself achieves an important beneficial and ethical outcome, an outcome that should be a priority of every intensivist.”[9]

Pain, sleep deprivation, and immobilization impair recovery. They sensitize the central nervous system, causing “wind-up,” which further amplifies pain and stress. This increases cardiac demand, vasoconstriction, blood viscosity, platelet aggregation, and cellular catabolism. In fact, “In many patients with severe posttraumatic of postsurgical pain, the ensuing neuroendocrine responses are sufficient to initiate or maintain a state of shock.”[10] Sometimes the pharmacologic analgesics and sedatives used to make patients comfortable can create other problems, such as constipation and disorientation. Certain complementary alternative medical interventions can offer safe and effective nonpharmacologic alternatives.[11]

Veterinary ICU personnel often welcome complementary alternative medical interventions that support the animals' quality of life and potentially improve survival. In human medicine, a 2005 survey published in the *American Journal of Critical Care* indicated that over 90% of critical care nurses reported eagerness or openness to using complementary alternative medical interventions in the ICU setting.[12]

165.3 ACUPUNCTURE

Acupuncture works by stimulating nerve endings near acupuncture points, sending afferent volleys into the central nervous system (CNS). The resultant input acts on certain brain and spinal cord regions to modulate neural output to both somatic and visceral structures. It also helps restore balance between the sympathetic and parasympathetic limbs of the autonomic nervous system. Acupuncture causes changes in neurotransmitter and hormone levels in the CNS, activating endogenous pain control mechanisms and decreasing anxiety.

Indications for acupuncture therapy in hospitalized patients include resuscitation (Color Plate 165-1); acute and chronic pain; muscle tension, tremors, and contractures; anxiety; neuropathy and neuropathic pain; stroke; functional gastrointestinal (GI) disorders such as nausea and vomiting, esophageal spasm, posttraumatic and postoperative ileus, gastric hyperacidity, diarrhea, and constipation; phantom pain; spine-related pain; pain from arthritis, bursitis, tendonitis, sprains, fractures, and contusions; edema; circulatory abnormalities; sinusitis; hiccoughs; urinary incontinence or retention; and acupuncture-assisted anesthesia for high-risk patients.[13]

Relative contraindications to acupuncture include severe immune compromise, bleeding disorders, widespread skin infections, pacemakers, and pregnancy.

165.4 MASSAGE AND OTHER FORMS OF GENTLE MANUAL THERAPY

Massage, or gentle, rhythmic stroking, can reduce stress, alleviate discomfort stemming from tension and immobility, and help normalize physiologic function.[14-18] The comfort massage provides can promote sleep, a vital restorative process.[19] Pulmonary function may improve after vibratory massage.[20] Patients with burn injuries and scarring may also benefit from massage.[21,22] Contraindications to massage depend on the patient's medical status and receptivity to touch. Patients with an cardiovascular instability or severe, uncontrolled hypertension may become overstimulated.[23,24] Massage should be avoided near sites of fractures, contusions, thrombi, inflammation, and infection.

165.5 PHYSICAL THERAPY OR REHABILITATIVE APPROACHES

Simple rehabilitative maneuvers such as passive range of motion and assisted weight bearing or ambulation may aid in preserving joint health, muscle mass, respiratory muscle strength, and endurance in severely ill animals.[25] Certain measures may also reduce lymph accumulation and improve quality of life for ICU patients.[7]

If nonveterinarians (such as physical therapists trained to work with humans) provide rehabilitative care for critically ill patients, veterinary supervision is required. This allows the veterinarian in charge of the animal's care to observe the animal undergoing the therapy and to intervene immediately if injury ensues or is likely. Unlike human physical therapy, animal rehabilitation is a young field. Even the human physical therapy field has a need for more high-quality evidence to support its interventions[26]; physical therapy for animals has almost none.

Cryotherapy (ice packs, gel packs, braces with circulating ice water) following orthopedic surgery does appear to significantly reduce postoperative pain in some cases, although not all.[27,28] Pulsed electromagnetic field therapy in conjunction with ice may augment pain control and range of motion over either method alone.[29] Physical therapists have used superficial heat applications since at least the 1950s, although this may have more value in relaxing tense muscles than increasing flexibility.[30] Deep heating approaches such as therapeutic ultrasonography and diathermy have been advocated for conditions such as tendinitis, skeletal muscle tension, and wound healing.[31] Incorrect applications of either superficial or deep heat may cause burns. Ice application may cause frostbite or neurologic compromise of superficial nerves.[32]

Practitioners should monitor animals closely for pain or discomfort. Extra caution is required when treating animals with compromised sensation (subsequent to neurologic injury, anesthesia or sedation, or treatment with cold packs or ice), that may not react when the treatment is burning viable tissue.[33] Veterinarians must weigh the negative consequences of shaving critically ill patients to prepare them for ultrasonography against the potential benefits of deep-tissue heating. Therapeutic ultrasonography should be avoided over pacemakers, joints, reproductive organs, the carotid sinus, cervical sympathetic ganglia, the eyes, heart, spinal cord (post laminectomy), tissue near a bone fracture or bony prominences, methyl methacrylate compounds, epiphyses in growing animals, tumors, and contaminated wounds.

Electrical stimulation, such as neuromuscular electrical stimulation therapy, is the application of an electrical current that elicits muscle contraction. It may be indicated for muscle tension, muscle atrophy, and neuromuscular reeducation. Pulsed signal therapy is another technique that attempts to reactivate chondrocytes and connective tissue and has been used for wound healing and other injuries. However, some animals find strong electrical stimulation aversive, and its role in veterinary ICU patients remains undetermined. Electrical stimulation should be avoided in patients with a pacemaker, thrombus, infection, or neoplasm in the treatment region. As noted above, extra caution is required for animals with compromised sensation, that may not verbalize when the intervention is causing pain or injuring tissue.

Hydrotherapy is frequently recommended for patients recovering from neurologic or orthopedic injuries or surgery. 717
However, it would be ill advised for patients that dislike water activities. Underwater treadmills provide footing for 718
animals, whereas immersion in pools or tanks may cause animals to thrash and injure themselves unless closely monitored. Water temperature should be adjusted to the animal's individual requirements to avoid overheating or hypothermia. Deconditioned animals can soon become fatigued. As such, vital signs should be evaluated on a regular basis during exercise. Tanks, pools, and underwater treadmills should be disinfected meticulously to prevent cross-contamination between patients.

165.6 HERBS

Veterinarians treating critically ill patients often find themselves in the difficult position of either accommodating or denying clients' requests to give herbs and supplements, with little substantive information on which to base the decision. In some cases, an herb's contents may be unknowable, as in the case of *yunnan paiyao,* a secret Chinese herbal mixture thought to contain mainly ginseng and used both to stop hemorrhage and to restore normal blood flow. Acquiescing to a client's request to administer *yunnan paiyao* preoperatively or postoperatively places a clinician in the unenviable position of uncertainty should a bleeding or clotting disorder arise.

Herbs pose several hazards because of the vast unknowns regarding species-specific metabolism, alterations in pharmacodynamics and pharmacokinetics in the critically ill patient, and unforeseen drug-herb interactions.[34] Botanical substances that affect neurotransmitters, such as serotonin in the case of St. John's wort and γ-aminobutyric acid in valerian root, can cause excessive sedation when combined with barbiturates, opiates, or other psychoactive medications. Common herbs such as ginkgo, ginseng, garlic, and *dong quai* may promote bleeding by inhibiting platelet function. Trauma or postoperative patients who have been receiving these herbs before entering the clinic may exhibit unexpectedly heavy bleeding. Unanticipated potentiation of anticoagulants is another potential outcome.[35] Various western and Asian plant products affect blood sugar levels; these include *Gymnema,* psyllium, fenugreek, bilberry, garlic, ginseng, dandelion, burdock, prickly pear cactus, and bitter melon.[36] Clinicians need to take into account clients' prior coadministration of herbs with insulin in order to optimize glucose control during hospitalization.

Many other herbs cause adverse effects or drug-herb interactions; insufficient research exists to fully evaluate all concerns regarding these products.[37]

165.7 PROBIOTICS

Probiotics, or “good” bacteria for the gut, offer unique benefits for the host by modulating GI microflora. They provide antiinflammatory, antiinfective, and immune-boosting effects, but their benefits in critically ill patients remain unclear. Limiting the growth of putative pathogens in the gut has been proposed as a means to reduce bacterial translocation, intestinal inflammation and, as a result, systemic illness.[38] However, whether administration of probiotics will actually influence the rate of bacterial translocation or postoperative septic morbidity in critically ill or postoperative veterinary patients remains to be proven.[39,40] As with herbs and nutritional supplements, the lack of consistency between labels and contents of probiotics remains a pressing concern.[41] Some asthmatic cats may develop bronchoconstriction in response to aromatherapy.

165.8 AROMATHERAPY

Aromatherapy may play a supportive role in the ICU, although subjecting all animals and staff to volatile substances may become problematic. For example, inhaled oil of lavender is soporific and antinociceptive.[42] Passion flower *(Passiflora)* is also sedating.[43] Oils with high levels of camphor can reportedly promote seizures and as such should be avoided in epileptic patients.[44] Some asthmatic cats may develop bronchoconstriction in response to aromatherapy.

165.9 ENERGY WORK

Numerous approaches fall under the heading of *energy work*. These include Reiki, Healing Touch, Therapeutic Touch, homeopathy, and flower essence therapy (homeopathic dilutions of flower petals soaked in water and sunlight). They all require further research to determine their effectiveness in veterinary ICU patients. Although these therapies are unlikely to cause harm, nonveterinarians providing these interventions should be instructed in infection control procedures before gaining entry to the veterinary ICU.

165.10 GLANDULAR SUPPLEMENTS

Certain holistic practitioners prescribe “glandulars” (desiccated animal tissues or glands) for animals experiencing organ failure or compromise. The simple premise underlying glandular therapy holds that animals with organ dysfunction should receive supplements consisting of that same organ tissue from healthy animals. These practitioners make the unsupportable assumption that neural and glandular components sold by supplement companies that have been salvaged from slaughterhouse carcasses (usually bovine or porcine) are free of disease and infection. Glandulars are unregulated and can contain active hormones, contaminants, or diseased tissue and have no place in the treatment of ICU patients.

165.11 SUMMARY

Not all complementary therapies belong in the critical care setting. Careful analysis of the individual patient's needs, client expectations, practitioner availability, along with clear-cut goals for improving quality of life and speed of recovery will help veterinarians develop a well-planned, integrative approach.

165.12 SUGGESTED FURTHER READING*

RE Gompf: Nutritional and herbal therapies in the treatment of heart disease in cats and dogs. *J Am Anim Hosp Assoc*. **41**, 2005, 355, *Paper that provides an excellent review of the potential benefits and adverse effects of supplements used in the treatment of heart disease in cats and dogs. Highly recommended.*

LA Lamont, WJ Tranquilli, KA Grimm: Physiology of pain. *Vet Clin North Am Small Anim Pract*. **30**, 2003, 703, *A chapter that provides a compelling compilation of why veterinarians must identify and treat pain in animals*.

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* See the CD-ROM for a complete list of references.

166 Chapter 166 Hypothermia

Jeffrey Todd, DVM

Lisa Leigh Powell, DVM, DACVECC

166.1 KEY POINTS

- Hypothermia causes severe cardiovascular, respiratory, electrolyte, nervous system, acid-base, and coagulation abnormalities.
- Early and aggressive treatment can decrease morbidity and mortality in the critically ill patient.
- Rewarming shock is a common complication, resulting from peripheral vasodilation when the periphery is warmed before the core.
- Therapeutic hypothermia in cardiac arrest and for neuroprotective properties appears promising and is being investigated.[1]

166.2 INTRODUCTION

Hypothermia is a condition in which the core body temperature is below the normal physiologic parameters for an individual species. Any condition or state that causes increased heat loss, decreased heat production, or a disruption of normal thermoregulatory function can lead to hypothermia. Because core temperature fluctuates mildly throughout the day, a range of normal temperatures for dogs and cats of 37.5° to 39.2° C (99.5° to 102.5° F) and 37.8° to 39.5° C (100° to 103.1° F), respectively, has been established.

Hypothermia is a relatively common condition in the emergency setting, with significant deleterious effects to the patient. Cardiovascular, respiratory, electrolyte, nervous system, acid-base, and coagulation abnormalities are commonly noted and should be anticipated. Early and aggressive treatment of hypothermia can decrease morbidity and mortality in the critically ill patient.

Renewed interest in therapeutic hypothermia for the treatment of traumatic brain injury and hemorrhagic shock has shown promising results. Studies in humans have shown that mild therapeutic hypothermia can improve outcome from several ischemic and traumatic insults.[2]

166.3 CLASSIFICATION

Hypothermia is classified as either a primary or secondary condition. Primary hypothermia, or “accidental” hypothermia, is a subnormal temperature caused by excessive exposure to low environmental temperature. Secondary hypothermia is a result of disease, trauma, surgery, or drug-induced alteration in heat production and thermoregulation.[3] In animals, severity of hypothermia is classically graded as mild—32° to 37° C (90° to 99° F), moderate—28° to 32° C (82° to 90° F), and severe—less than 28° C (82° F).[4] Patients with secondary hypothermia have more profound clinical signs at higher temperatures than do patients with primary hypothermia. Therefore a novel grading system has been proposed to describe patients with secondary hypothermia: mild—36.7° to 37.7° C

(98° to 99.9° F), moderate—35.5° to 36.7° C (96° to 98° F), severe—33° to 35.5° C (92° to 96° F), and critical—less than 33° C (92° F).[3]

166.4 THERMOREGULATION REVIEW

A normal core temperature is maintained by an intricate balance of metabolic heat production and heat loss. The main thermostat of the body is the hypothalamus, with temperature changes sensed by the preoptic and anterior hypothalamic nuclei. Secondary temperature sensors are located within the skin and deep body tissues, namely, the spinal cord, abdominal viscera, and great veins.[5]

Most of the heat generated is by the most metabolically active systems, the brain, truncal organs, and active muscles.[5,6] The rate of heat production is dependent on the metabolic rate of the body, maintained by basal and accelerated cellular metabolism. Increased metabolic rate is achieved in response to thyroxine, epinephrine, norepinephrine, sympathetic stimulation, and muscle contraction secondary to shivering.[5]

Heat production without heat retention would be an ineffective means of increasing and maintaining core body temperature. Therefore heat retention plays an integral role in physiologic homeostasis. Heat retention is achieved by both behavior responses, huddling and curling, and reflex physiologic changes such as piloerection and peripheral vasoconstriction.[4] A failure of adequate heat production or retention will lead to hypothermia.

Heat loss is required to prevent hyperthermia, but it can be detrimental to the patient when in excess. There are four main mechanisms of heat loss in the veterinary patient: convection, conduction, radiation, and evaporation.[3] In animals, most heat loss is through convection and conduction. This is in contrast to humans, where most heat loss is a result of radiation.[7]

- *Convection* is the transfer of heat from the body surfaces to air surrounding the body.
- *Conduction* is the transfer of heat from body surfaces to objects that come into contact with the body, such as the ground, examination tables, and kennels.
- *Radiation heat transfer* is the loss of heat to surrounding structures that do not come into direct contact with the body, such as walls.
- *Evaporative heat transfer* is the loss of heat from moisture on the body surfaces or through the respiratory tract to the environment.[3]

Many factors contribute to the degree of heat loss. Neonates have large surface areas that accelerate heat loss. 720
Cachectic patients have decreased fat and muscle stores that allow faster heat transfer, because fat is an excellent 721
insulator. Severely debilitated patients have a decreased ability to respond to hypothermia, either due to the inability to seek and retain heat or to mount an appropriate physiologic response.

166.5 PHYSIOLOGIC EFFECTS OF HYPOTHERMIA

Hypothermia may cause serious, deleterious effects on the body. These complications can be anticipated based on the degree of hypothermia and the known physiologic effects at those temperatures. It follows that the most serious effects are found in patients with the most profound hypothermia. Cardiovascular, respiratory, neurologic, and metabolic changes are commonly encountered.

166.5.1 Cardiovascular Effects

The cardiovascular changes found in hypothermia include bradycardia, hypotension, cardiac arrhythmias, decreased cardiac output, and asystole. The initial cardiovascular effects with mild hypothermia are an increase in heart rate and arterial blood pressure. This is mediated by catecholamine release secondary to stimulation of the autonomic nervous system.[6] As hypothermia progresses, α_1-receptor affinity for norepinephrine begins to decrease, leading to a diminished contractile response. At this point, normal vasoconstriction is lost and arterial vasodilation occurs, contributing to hypotension and decreased cardiac output.[3]

Hypothermia may also cause a shift to the left in the oxygen-hemoglobin dissociation curve, resulting in tissue hypoxia. This, in combination with cutaneous vasoconstriction causing arteriovenous shunting, leads to peripheral hypoxia or dysoxia, causing an increase in systemic vascular resistance.[6]

Bradycardia develops with mild hypothermia (36° C or 96.8° F), a result of decreased spontaneous depolarization of cardiac pacemaker cells. Consequently, the bradycardia is refractory to atropine administration.[6] In humans, hypothermia causes a pathognomonic Osborn, or J, wave, which is an acute ST segment elevation at temperatures of 32° to 33° C (90° to 92° F). This has rarely been documented in small animals.[4] Electrocardiographic changes in veterinary patients include lengthened PR intervals, QRS complexes, and QT intervals. As temperatures approach 23.5° C (74.3° F), 50% of dogs demonstrate ventricular fibrillation.[8]

166.5.2 Respiratory Effects

The pulmonary effects of hypothermia include decreases in respiratory rate and depth, pulmonary tissue injury, and oxygen dissociation disturbances. Decreased cellular metabolism and lowered carbon dioxide production reduce the stimulus for respiration, leading to lower tidal volumes and respiratory rates.[6] Carbon dioxide production will decrease 50% with an 8° C (10.8° F) fall in body temperature.[7] As hypothermia progresses, pulmonary edema, bronchopneumonia, and decreases in mucociliary activity may lead to acute respiratory distress syndrome.[4] Additionally, a shifting of the oxygen-hemoglobin dissociation curve to the left further exacerbates the tissue hypoxia.

166.5.3 Neurologic Effects

Decreased mentation that culminates in unconsciousness is a common finding in patients with hypothermia. In humans, cerebral metabolism drops 6% to 7% for each degree Celsius decrease in core temperature.[3] The decreased cerebral metabolism allows the patient to meet metabolic demands for awhile, even during asystole.[7] The altered cerebral electrical activity with hypothermia will elicit a flat electroencephalogram with core temperatures of 19° to 20° C (66° to 68° F).[7] The combination of unconsciousness and severe bradycardia or asystole can lead to a misguided diagnosis of death in a live patient with severe hypothermia.

166.5.4 Metabolic Effects

Renal, hepatic, acid-base, immunologic, and coagulation complications may also be encountered in the hypothermic patient. The initial renal effect observed in mild to moderate hypothermia is diuresis, despite hydration status. This is often referred to as *cold diuresis*. [4] This occurs as a result of an initially sensed increased blood volume caused by peripheral vasoconstriction. This perceived hypervolemia results in a decreased production of antidiuretic hormone and subsequent increased glomerular filtration rate. This inappropriate diuresis can lead to severe dehydration and azotemia. As hypothermia progresses, decreased renal blood flow, decreased glomerular filtration rate, and ischemia can ultimately result in acute tubular necrosis and acute renal failure.[6]

The hepatic consequence of hypothermia is primarily related to the decreased hepatic enzyme activity leading to decreased metabolism of substances. The significance of this change will be most notable when anesthetic agents are required.[3] In a prospective human study, 40 minutes of additional postanesthetic recovery time was encountered for each 2° C decrease in core body temperature.[9]

Acidosis may develop with progressive hypothermia. This change is typically two-fold. If significant respiratory depression is present, a respiratory acidosis will develop from hypoventilation. Additionally, a metabolic acidosis may develop due to decreased tissue perfusion and increased muscle activity from shivering, which will lead to a lactic acidosis.[3,7]

Hypothermia causes direct impairment of primary immune functions, including impairment of chemotaxis and phagocytosis of granulocytes, decreased mobility of macrophages, and impaired oxidative killing by neutrophils. [10] In humans, an increased risk of infection and poor or delayed wound healing occurs secondary to hypothermic states.[6] A retrospective study in veterinary medicine found mild hypothermia not to be a significant risk factor for postoperative wound infection in clean surgical wounds.[11]

Hypothermia has dramatic effects on normal coagulation mechanisms. The primary changes are associated with an apparent thrombocytopenia, platelet dysfunction, coagulation factor activity, and disruption of fibrinolytic equilibrium.[12] Sequestration of platelets by the liver and spleen in hypothermia accounts for the quantitative platelet decrease. Platelet aggregation is disrupted by decreased production of thromboxane B_2, decreased platelet granule secretion, and diminished expression of the von Willebrand factor receptor.[12]

In addition to primary hemostatic changes, secondary hemostatic alterations are found on diagnostic coagulation tests, including prolonged prothrombin time and activated partial thromboplastin time. Of significant importance is the disparity between a clinically observed coagulopathy and a normal coagulation assay result. Warming the blood sample for the assay will often result in normal coagulation times, despite an obvious clinical coagulopathy.[12] When the patient is subsequently normothermic, the coagulation cascade can return to normal. Therefore the standard clotting tests run in the laboratory at 37° C (98.6° F) will not reflect the hypothermic effects on the clotting cascade.[7]

Finally, the additional complication of disseminated intravascular coagulation is observed because of impairment of intrinsic inhibitors of fibrinolysis.[12]

166.6 THERAPY

Therapy for hypothermia consists of appropriate rewarming of the patient, cardiovascular support, management of complications and comorbid disease, and prevention of further complications. The mainstays of therapy include intravenous fluid administration and rewarming.

166.6.1 Rewarming

The technique used for rewarming depends on the degree of hypothermia and the stability of the patient. In mild hypothermia, 32° to 37° C (90° to 99° F), passive rewarming of a stable patient will likely be effective. With passive rewarming, the patient's own intrinsic heat production mechanisms are augmented, typically by wrapping in insulating blankets. All hypothermic patients should be rewarmed passively to prevent further heat loss and to enhance other warming modalities.

In moderate hypothermia, 28° to 32° C (82° to 90° F) or an unstable mild hypothermia, a more aggressive approach is required. Active external rewarming is employed by any technique that transfers heat to the patient, including hot water blankets, heat lamps, and forced air warmers. Direct contact between radiant warming devices and the skin must be prevented, because the vasoconstricted skin is unable to conduct heat away, leading to burn injuries.[7] Initial heating by these methods should be aimed at the trunk instead of the extremities. The extremities will become heated by the warmed blood returning from the heart when perfusion is restored. If the extremities are rewarmed initially, peripheral vasodilation can result in rewarming shock. This shock results from the pooling of warm blood in the extremities with return of cool blood to the heart, causing hypotension.[6]

In severe hypothermia, less than 28° C (<82° F), active core rewarming is indicated. Warm intravenous fluids and pleural and peritoneal lavage are common techniques. The lavage fluids, either stock dialysate or isotonic crystalloids, are warmed to 40° to 45° C (104° to 113° F). The fluids are then infused through aseptically placed pleural or peritoneal catheters at 10 to 20 ml/kg per exchange.[13] Another technique, administering warmed humidified air or oxygen via face mask or endotracheal tube, can increase the body temperature 1° to 2° C each hour.[14] Irrigation of the stomach, colon, and urinary bladder is of questionable value because of the limited surface area of these structures.[7]

166.7 THERAPEUTIC HYPOTHERMIA

Renewed interest in induced or prolonged hypothermia as a therapeutic agent has shown promise in a number of disease states.[15] The most widely accepted use of hypothermia is for its neuroprotective properties after cardiac arrest and subsequent return of spontaneous circulation. A large body of evidence supports the use of hypothermia to prevent or limit damage to the injured brain.[15] This protection is thought to be due to the prevention of apoptosis after cellular injury. In humans, following witnessed cardiac arrest in the intensive care unit, only 10% to 20% are discharged alive without significant neurologic deficits. One study reported significant improvements in neurologic outcome in human hypothermic patients compared with normothermic patients, although there were no significant differences in survival.[15] In a veterinary study, mild or moderate hypothermia during prolonged cardiopulmonary-cerebral resuscitation in dogs improved outcome and preserved extracerebral organ viability.[16]

An additional area of interest for therapeutic hypothermia is hemorrhagic shock. Laboratory studies of hemorrhagic shock in pigs showed improved survival when patients were kept mildly hypothermic. In exsanguinating hemorrhage, hypothermic suspended animation via aortic flush may allow survival in typically lethal situations.[2] Although laboratory evidence is promising, the clinical applications of hypothermia are still being investigated and additional research is required.

166.8 SUGGESTED FURTHER READING*

SR Armstrong, BK Roberts, M Aronsogn: Perioperative hypothermia. *J Vet Emerg Crit Care*. **15**, 2005, 32, *An excellent clinical practice review of the physiologic changes associated with hypothermia in general, as well as those related specifically to the perioperative period.*

A DeLaforcade, N Dhupa, I Hypothermia: Pathophysiology. In RJ Murtaugh, N Dhupa (Eds.): *Critical care quick look series*. 2002, Teton NewMedia, Jackson Hole, WY, *A very short and succinct review of the pathophysiology of hypothermia aimed primarily as a quick reference*.

AK Oncken, R Kirby, E Rudloff: Hypothermia in critically ill dogs and cats. *Comp Cont Educ Small Anim Pract*. **23**, 2001, 506, *An extremely well written and easy to follow review of hypothermia in the small animal species*.

WE Wingfield: Accidental hypothermia. In WE Wingfield, MR Raffe (Eds.): *Veterinary ICU book*. 2002, Teton NewMedia, Jackson Hole, WY, *An extremely thorough and easy to understand review of current concepts in hypothermia and therapeutic recommendations*.

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* See the CD-ROM for a complete list of references.

167 Chapter 167 Heat Stroke

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167.1 KEY POINTS

- Heat stroke is the most serious condition of heat-induced illnesses.
- Heat stroke can be classified as exertional (overheating while exercising) and nonexertional (classic heat stroke).
- Heat stroke is generally associated with multiorgan derangements, but central nervous system dysfunction (ranging from mild to moderate altered mentation to seizures or coma) is the hallmark of the condition.
- Every system can be affected, but the major ones include the cardiovascular, central nervous, gastrointestinal, renal, and coagulation systems.
- Treatment involves cooling the patient followed by supportive care.
- In human medicine and experimental dog models, no cooling method has proved superior to others.
- A worse prognosis in dogs has statistically been associated with hypoglycemia, decreased cholesterol, increased bilirubin, and decreased albumin levels, ventricular arrhythmias, and increased creatinine values.

167.2 INTRODUCTION

Three syndromes of heat illness that represent a continuum from the least to the most severe form are described in humans. Heat cramp is characterized by muscle spasms resulting from sodium and chloride depletion. When signs such as fatigue, weakness, muscle tremors, vomiting, and diarrhea occur, heat prostration or exhaustion may be diagnosed. The hallmark of heat stroke is severe central nervous system (CNS) disturbance and is often associated with multiple organ dysfunction. A more recent definition of heat stroke describes it as a form of “hyperthermia associated with a systemic inflammatory response leading to a syndrome of multiorgan dysfunction in which encephalopathy predominates.”[1] This latter definition is more physiologically based and gives a much more informative description of what is seen clinically in dogs with heat stroke. Generally, clients seek veterinary attention when their pets are demonstrating signs consistent with heat prostration, heat exhaustion, or heat stroke. This chapter will focus primarily on dogs with heat-induced illness because cats rarely suffer from heat stroke.

167.3 PHYSIOLOGY, PATHOGENESIS, AND PATHOPHYSIOLOGY

A hot environment or exercise in a hot environment does not equate to overheating and heat-induced illness. It is the increase in core body temperature that results in heat-induced illness (see Chapter 5, Hyperthermia and Fever). Therefore the body has developed a relatively effective thermoregulation system to protect itself from overheating.

Thermal homeostasis is maintained by a balance between heat load (environmental heat and heat generated through metabolism and exercise) and heat-dissipating mechanisms controlled by temperature-sensitive centers in the hypothalamus. Body temperature increases when heat load exceeds heat dissipation. Heat dissipation may occur via four mechanisms: convection, conduction, radiation, and evaporation. As the body temperature increases, 70% of heat loss in dogs and cats occurs via radiation and convection through the skin. Heat loss is facilitated by increased cutaneous circulation as a result of increased cardiac output and sympathetic-mediated peripheral vasodilation.[2] Shunting of blood to the periphery is a trade-off with blood supply to the viscera (intestines and kidneys). Significant heat loss also occurs as a result of evaporation from the respiratory tract through panting, and this becomes the predominant mechanism of heat loss when ambient and body temperatures become equal.

A warm, humid environment and exercise are the two most common heat loads that dogs experience and may cause extreme hyperthermia, even in animals with functional heat dissipating mechanisms. Respiratory evaporative heat loss may be diminished by humid climatic conditions, closed confinement with poor ventilation, and upper respiratory abnormalities such as brachycephalic conformation, laryngeal paralysis or masses, or collapsing trachea. Additionally, the work of breathing in these latter conditions can contribute substantially to the heat load in these animals. Diminished radiation and convective heat loss from the skin may occur as a result of hypovolemia from any cause, poor cardiac output, obesity, extremely thick hair coat, or lack of acclimatization to heat. Situations that combine high heat load and diminished heat dissipation may result in a rapid and extreme body temperature increase.

Most dogs with heat illness present when the warm, humid weather begins, so the seasonal pattern varies depending on climatic conditions and year-to-year variations in temperature and humidity. In some instances, despite progressively warmer days later in the summer, heat-induced illness becomes less frequent.[3] This may be related to the time available for acclimatization to the change in environmental temperature. In humans, acclimatization to heat can take 2 weeks or more and is associated with enhanced cardiac performance, salt conservation by the kidney and sweat glands through activation of the renin-angiotensin-aldosterone axis, an increased capacity to sweat, plasma volume expansion, increased glomerular filtration rate, and an increased ability to resist exertional rhabdomyolysis.[4]

Increased body heat induces three protective mechanisms, including thermoregulation (mentioned previously), an acute phase response, and intracellular heat shock proteins.[1] The acute phase response involves a variety of proinflammatory and antiinflammatory cytokines. Proinflammatory mediators induce leukocytosis, stimulate synthesis of acute phase proteins, stimulate the hypothalamic-pituitary-adrenal axis, and activate endothelial cells and white blood cells. These mediators are protective for the body when balance is maintained between the proinflammatory and antiinflammatory sides. 723 724

The heat shock proteins protect the cell and the body against further heat insults, likely as a result of protection against denaturation of intracellular proteins and regulation of the baroreceptor response during heat stress, preventing hypotension and conferring cardiovascular protection.[5] Heat stroke results from a failure of thermoregulation followed by an exaggerated acute phase response and alteration of heat shock proteins.[1] Additionally, absorption of endotoxin from the gastrointestinal (GI) tract may fuel the inflammatory response, because intestinal mucosal permeability is increased during heat stress.[6] It has been noted that many of the mediators involved in heat stroke are the same mediators associated with sepsis and the systemic inflammatory response syndrome (see Chapters 11 and 106, Systemic Inflammatory Response Syndrome and Sepsis, respectively).[1]

The suggested pathophysiologic sequence in heat stroke involves initial production and release of interleukin-1 and interleukin-6 from the muscles into the circulation and increased systemic endotoxin from the intestines.[1] These factors mediate excessive activation of leukocytes and endothelial cells, resulting in release of numerous inflammatory and antiinflammatory cytokines, as well as activation of coagulation and inhibition of fibrinolysis. Direct endothelial cell injury due to the heat, combined with an initial hypercoagulable state, result in microthrombosis and progressive tissue injury. These proinflammatory and procoagulation processes and direct heat injury can lead to multiple organ dysfunction syndrome. Because of the multisystemic problems in patients with heat stroke, these animals should be assessed and monitored for multiple organ failure, particularly the respiratory, cardiovascular, renal, GI, and central nervous systems, as well as the coagulation system.

167.4 PHYSICAL EXAMINATION

The physical findings of dogs suffering from heat-induced illness vary with the intensity and duration of the increased body temperature and the individual pathophysiologic responses that are initiated.

167.4.1 Temperature, Pulse, and Respiratory Rate

The rectal temperature may be decreased, normal, or increased depending on tissue perfusion and whether cooling measures have already been implemented. The pulse rate is usually increased as a result of compensatory sinus tachycardia. The respiratory rate is very rapid, usually to improve heat dissipation rather than as a result of respiratory disease.

167.4.2 Cardiovascular System

Most dogs arrive in a hyperdynamic state. The mucous membranes are usually hyperemic and the capillary refill time is very short. The pulses are often weak because of hypovolemia secondary to evaporative fluid loss, vomiting, diarrhea, and vasodilation. Sinus tachycardia is common. Rarely, some dogs have intermittent ventricular arrhythmias, which have been associated with a worse outcome in clinical cases of heat-induced illness.[3] Electrocardiographic evaluation and monitoring should be performed on all patients with severe heat-associated illness.

167.4.3 Respiratory System

Careful evaluation of the respiratory system is warranted, because evaporation through the respiratory tract is a major mechanism for heat dissipation. Loud or noisy breathing that is heard without the stethoscope suggests an upper airway abnormality such as laryngeal paralysis or edema, obstruction, or tracheal collapse. Careful auscultation for harsh airway sounds or pulmonary crackles should be performed. Many dogs with heat-induced illness have been vomiting, and aspiration pneumonia must be considered. Dogs suffering from disseminated intravascular coagulation (DIC, see Coagulation System) may have pulmonary parenchymal hemorrhage resulting in crackles or harsh airway sounds, although in a retrospective study of clinical heat stroke cases, pulmonary parenchymal abnormalities were not common.[3]

167.4.4 Central Nervous System

Mentation may range from alert to comatose, with depression being the most common abnormality. The severely affected dog will be comatose or stuporous at presentation. Pupil size may range from dilated to pinpoint, but are usually responsive to light. Some dogs may be cortically blind when they are presented, but that may resolve after several hours. Similarly, head bobbing or tremors occur transiently and resolve over hours. Ambulatory dogs may be ataxic. The cause of these neurologic abnormalities may include poor cerebral perfusion, direct thermal damage, cerebral edema, CNS hemorrhage, or metabolic abnormalities such as hypoglycemia or hepatoencephalopathy, although the latter has not been documented in clinical cases of dogs with heat stroke.

167.4.5 Renal System

Physical evaluation of the renal system is very limited. Palpation of bladder size and its change in size as fluid therapy ensues may be helpful in assessing urine production. Renal failure is a potential complication of heat stroke, and monitoring urine production is a valuable tool (see Chapter 135, Acute Renal Failure).

167.4.6 Gastrointestinal System

Many of the severely affected dogs have protracted vomiting and diarrhea. The diarrhea may range from watery to hemorrhagic with mucosal sloughing. This may occur secondary to DIC or poor visceral perfusion and reperfusion as volume resuscitation is provided. Gastric ulceration may occur as well, resulting in vomiting with or without blood.

167.4.7 Coagulation System

DIC is not an uncommon finding in dogs with heat-induced illness. The presence of petechiae and ecchymoses or blood in the urine, vomit, or stool suggests that DIC may be present (see Chapter 117, Hypercoagulable States).

167.5 LABORATORY EVALUATION

An initial database including packed cell volume, total solids, dipstick blood urea nitrogen (BUN) level, whole blood glucose concentration, and blood sodium and potassium levels should be obtained if possible. The packed cell volume and total solids are often elevated because of hemoconcentration. The dipstick BUN value may be increased, likely because of poor renal perfusion, although GI hemorrhage or renal failure must also be considered. The blood glucose concentration may be very low in the severely affected patient secondary to increased utilization from hyperthermia and/or early sepsis requiring intravenous supplementation. Sodium and potassium concentrations are generally normal in these patients on arrival but warrant evaluation, especially if vomiting and diarrhea have occurred or an acidosis or renal failure is suspected. In addition, excessive panting may quickly lead to hypernatremia due to a loss of free water.

Urinalysis should be performed, preferably before initiating fluid therapy, to assess renal function or damage; however, collection by cystocentesis should be avoided because of potential coagulation abnormalities. Urine specific gravity should be interpreted in light of the patient's hydration and perfusion status. Urine assessment by dipstick is often positive for protein and hemoglobin. Glucosuria may be detected despite normal or even low blood glucose levels, which may suggest proximal tubular damage or recent hyperglycemia with glucosuria. Urine sediment examination may reveal red blood cells, indicating renal damage or coagulation abnormalities. Renal casts indicate renal damage, warranting close monitoring of urine output and renal function.

Further laboratory evaluation should include a complete blood count, serum chemistry screen, serum creatinine kinase activity, and coagulation evaluation. The most common complete blood count abnormality that has been reported is increased nucleated red blood cells.[3] No prognostic significance has been associated with this finding, but it may be helpful in evaluating dogs that have experienced heat stroke several hours before presentation and present with an unknown history of heat exposure or overheating. The nucleated red blood cell level decreases rapidly after the first 24 hours.

Serum alanine aminotransferase and creatinine kinase are often elevated and usually peak within 24 to 48 hours. Serum bilirubin may be increased and serum cholesterol decreased in more severely affected dogs. Serum creatinine and BUN concentrations may be increased as well. These increases may be a result of dehydration and poor renal perfusion, but warrant serial evaluation, because renal damage may be present and serial increases in renal clinicopathologic parameters are associated with a worse prognosis.[3]

Activation of the coagulation cascade is initiated by direct thermal injury to the tissues and endothelium, and may result in consumption of platelets and coagulation factors. If prothrombin time, partial thromboplastin time, and platelet count cannot be performed, then an activated clotting time should be performed, and a blood smear may reveal red blood cell fragments and allow for an estimation of platelet count. In general, there should be at least 8 to 15 platelets per oil immersion field on a well-performed blood smear. In patients with DIC, the platelet count is often decreased secondary to increased consumption and/or loss.

167.6 TREATMENT AND MONITORING

167.6.1 Cooling Procedures

Cooling measures involve taking advantage of the physics of heat dissipating mechanisms: evaporation, conduction, convection, and radiation. Evaporative methods include whole body wetting of the dog with water and blowing fans over the body. In humans, ice water is used with this method, but recommendations are to massage the muscles to maintain circulation because extreme cooling of the periphery may result in vasoconstriction and paradoxical inhibition of body cooling. Whole body alcohol bathing should be avoided, because this may present a significant fire hazard should defibrillation be required in dogs that suffer cardiac arrest.

Intuitively, wetting the foot pads with alcohol, although not rigorously evaluated for its efficacy in cooling dogs, seems like it would not be a very effective cooling measure given the small surface area involved. External conduction cooling techniques include application of ice packs, tap water immersion, ice-water immersion, and cooling blankets. Water immersion methods can be cumbersome, and ice-water baths may be uncomfortable as well as produce peripheral vasoconstriction and diminish heat dissipation overall. Internal conduction techniques include iced gastric lavage and iced peritoneal lavage. These techniques are invasive and can result in serious complications (aspiration pneumonia, septic peritonitis). Pharmacologic techniques such as dantrolene sodium have been evaluated experimentally and have not been effective.[7]

Cooling measures are the only therapies for heat stroke that have been thoroughly evaluated. Many of the techniques already mentioned have been evaluated rigorously, both clinically in humans and experimentally in dogs. No technique has been proven superior to any other, and in dog experimental studies, temperature decline rates ranged from 0.15° to 0.23° C per minute.[8,9] Not surprisingly, many owners recognize that their dogs are overheated and hose them down with water. This is very effective and often results in a normal body temperature at presentation if the pet is presented immediately.[3]

Whole body wetting with water combined with muscle massage and blowing fans is commonly used. Additionally, administration of room temperature or cooled intravenous fluids may be helpful. Rarely, whole body shaving is needed to facilitate cooling in dogs with very thick hair coats. Cooling measures should be discontinued when the rectal temperature reaches 103° F to prevent rebound hypothermia. Despite this, it is not unusual for dogs to develop body temperatures between 95° to 100° F within the first few hours of hospitalization.[3] If hypothermia occurs, warm water bottles or blankets may be necessary to maintain normothermia.

167.6.2 Cardiovascular System

The severely affected dog often presents in hypovolemic shock. If cardiovascular disease is unlikely, cool balanced electrolyte fluids of up to 90 ml/kg should be administered intravenously to dogs (up to 50 ml/kg in cats) and a continuous assessment of perfusion status with titration of the rate and volume of fluids to effect should be performed (see Chapter 65, Shock Fluids and Fluid Challenge). Central venous pressure monitoring will help guide fluid therapy if massive volumes are required, although this usually requires jugular venous catheterization, which is contraindicated in dogs with severe coagulation derangements. If large doses of intravenous fluids do not improve tissue perfusion and blood pressure, administration of synthetic colloids should be considered, with or without positive inotropic or vasopressor agents (such as dobutamine, dopamine, or epinephrine). Dogs that cannot maintain an adequate blood pressure without pressure support (for prolonged periods) carry a poor prognosis. Blood pressure and physical parameters of tissue perfusion should be monitored continuously in severely affected dogs.

167.6.3 Respiratory System

Oxygen should be administered at presentation and should be continued until it has been determined that the dog can maintain adequate arterial oxygenation. Serial physical assessment of the respiratory system via auscultation, respiratory rate and effort, and mucous membrane color is warranted in the dog with heat illness. More objective assessments such as arterial blood gas analysis and pulse oximetry may be required, especially in dogs with physical evidence of respiratory compromise.

167.6.4 Central Nervous System

At presentation, a full neurologic examination, including level of mentation and cranial nerve function, should be performed to establish a baseline. The more severely affected dogs may present stuporous or comatose. Serum electrolytes, packed cell volume, total solids, and blood glucose measurements should be performed and abnormalities corrected as warranted. Hypoglycemia is not unusual in the severely compromised dog with heat illness. An intravenous bolus of 0.25 to 0.5 g/kg of body weight of dextrose should be administered (if hypoglycemia is documented) and dextrose added to the intravenous fluids to make a 2.5% to 5% concentration if hypoglycemia is persistent.

Poor tissue perfusion should be corrected and mentation reevaluated after perfusion is improved. If mentation continues to be abnormal after correcting these abnormalities, then cerebral edema may be present (see Chapter 100, Intracranial Hypertension). Mannitol (0.5 to 1 g/kg body weight IV over 20 to 30 minutes) should be considered. The head should be slightly elevated (15 to 30 degrees above horizontal) while avoiding compression of the jugular veins. Progression of neurologic abnormalities despite therapy carries a poor prognosis.

167.6.5 Renal System

A urinary catheter should be inserted at presentation for monitoring urine output in the more severely affected dog. Complete urinalysis should be performed initially and serially as treatment progresses to detect early signs of renal damage such as urinary casts. Urine output should be maintained at 2 ml/kg body weight/hr or greater, depending on the amount of fluid being administered. Mean arterial pressure ideally should be at least 80 mm Hg. If urine output remains insufficient despite adequate fluid replacement, then measures to manage oliguria or anuria should be instituted (see Chapters 7 and 135, Oliguria and Acute Renal Failure, respectively). If urine output remains inadequate with increasing renal parameters, hemodialysis or peritoneal dialysis may be instituded (see Chapter 137, Hemodialysis and Peritoneal Dialysis). Serum sodium, potassium, total solids, BUN, acid-base status, and creatinine should be monitored.

167.6.6 Coagulation System

Coagulation evaluation including prothrombin time, partial thromboplastin time, platelet count, and fibrin split products concentration should be obtained at presentation and as indicated during therapy. Prolonged coagulation, decreased platelet count, and increased fibrin split products or D-dimers suggest DIC (see Chapter 117, Hypercoagulable States). Thromboelastography may also prove useful, if available.

167.6.7 Gastrointestinal System

Direct thermal damage and poor visceral perfusion and/or reperfusion may result in GI mucosal sloughing and ulceration. This results in vomiting and diarrhea that may or may not be bloody. Sucralfate (if vomiting is not present) and histamine-2 blockers will help manage gastric ulceration (see Chapter 181, Gastrointestinal Protectants). Breakdown of the mucosal barrier may result in bacteremia or endotoxemia. Broad-spectrum antibiotics should be considered in severely affected animals with bloody diarrhea. Anecdotally, small intestinal intussusceptions develop in some dogs with heat stroke.

167.7 PROGNOSIS

The degree of compromise depends on the prior physical health of the dog and the degree and duration of the heat insult. Dogs with multiple organ dysfunction or severe CNS disturbance warrant a more guarded prognosis.[3] Alternatively, dogs with severe CNS disturbance, DIC, and other organ dysfunction live without any residual problems. Severe heat-induced illness is challenging to treat, but with aggressive medical therapy dogs may recover and do well. Since cats rarely develop heatstroke, there is little information regarding the prognosis and outcome in this species.

167.8 SUGGESTED FURTHER READING*

WS Fluornoy, JS Wohl, DK Macintire: Heatstroke in dogs: pathophysiology and predisposing factors. *Comp Cont Educ Pract Vet*. **25**, 2003, 410, *An excellent veterinary review of heat stroke*.

E Hadad, M Rav-Acha, Y Heled, et al.: Heat stroke: A review of cooling methods. *Sports Med*. **34**, 2004, 501, *An excellent review of the literature regarding the efficacy of various methods of cooling including water immersion, evaporative cooling, ice pack application, invasive cooling techniques, pharmacologically induced cooling, and other methods. Also includes this information on canine models*.

* See the CD-ROM for a complete list of references

168 Chapter 168 Anaphylaxis

Patricia M. Dowling, DVM, MS, DACVIM, DACVCP

168.1 KEY POINTS

- Anaphylaxis is a potentially fatal immunoglobulin E (IgE)-mediated hypersensitivity reaction.
- Anaphylactoid reactions are not IgE mediated, but they are clinically indistinguishable from anaphylactic reactions and treatment is the same.
- Anaphylaxis can be triggered by insect and reptile venoms, foods, vaccines, antimicrobial agents, and other drugs.
- In dogs, the anaphylactic *shock organ* is the liver, and in the cat it is the respiratory tract. Dermal and ocular manifestations may occur in both species.
- Although epinephrine is recommended as the treatment of choice for anaphylaxis, its efficacy in reversing the cardiovascular derangements in a canine model once full-blown shock has developed has been demonstrated only with continuous intravenous administration.
- Antihistamines (histamine-1 [H_1], H_2, and H_3 blockers) and glucocorticoids are adjunct treatments but their effects are delayed, so they are not helpful in patients in cardiovascular collapse or life-threatening bronchoconstriction.

168.2 INTRODUCTION

Anaphylaxis is a severe, potentially fatal hypersensitivity reaction and may involve multiple organ systems, including the skin and eyes, respiratory tract, cardiovascular system, nervous system, and gastrointestinal (GI) tract (Box 168-1). Anaphylaxis can be triggered by a variety of antigens, but most commonly by insect and reptile venoms, antimicrobial agents, nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, opiates, vaccines, foods, and physical factors such as cold and exercise. Traditionally, hypersensitivity reactions were classified into four types: type I: immediate (immunoglobulin, [IgE]-dependent), type II: cytotoxic (IgG, IgM dependent), type III: immune complexes (IgG, IgM complex dependent), and type IV: delayed (T lymphocyte dependent).

Anaphylaxis was attributed to type I reactions, and anaphylactoid reactions were attributed to non–IgE-mediated reactions. However, it is now known that cytotoxic (e.g., blood transfusion reactions) and immune complex (e.g., complexes of IgG administered intravenously or intramuscularly) reactions can cause anaphylaxis.

An alternative classification system based on seven immunopathologic mechanisms with both protective and destructive functions has been proposed: (1) immune-mediated inactivation and activation reactions of biologically active molecules, (2) antibody-mediated cytotoxic or cytolytic reactions, (3) immune complex reactions, (4) allergic reactions, (5) T lymphocyte–mediated cytotoxicity, (6) delayed hypersensitivity, and (7) granulomatous reactions.[1] Several of these immunopathologic mechanisms might be actively causing anaphylaxis in a given patient.

168.2.1 Box 168-1 Clinical Signs of Anaphylaxis or Anaphylactoid Reactions

168.2.1.1 Dermal

- Erythema
- Pruritus
- Urticaria
- Angioedema
- Maculopapular rash

168.2.1.2 Gastrointestinal

- Nausea
- Vomiting
- Diarrhea

168.2.1.3 Cardiovascular

- Tachycardia
- Hypotension
- Arrhythmias
- Myocardial ischemia
- Cardiac arrest

168.2.1.4 Respiratory

- Nasal congestion

Sneezing

Stridor

Oropharyngeal or laryngeal edema

Cough

Dyspnea

Bronchospasm

Tachypnea

Abdominal breathing

Cyanosis

Respiratory arrest

168.2.1.5 Neurologic

Weakness

Syncope

Seizures

168.2.1.6 Ocular

Pruritus

Conjunctival injection

Lacrimation

168.3 PATHOPHYSIOLOGY

In murine models, two immunologic pathways of anaphylaxis have been identified. One pathway involves IgE
receptors, mast cells, basophils, histamine, prostaglandins, leukotrienes, serotonin, and platelet-activating factor. A 727
second pathway involves IgG, Fcγ, macrophages, and platelet-activating factor.[2] With immune-mediated 728
anaphylaxis, previous exposure to an antigen results in sensitization, and IgE is produced and bound to the cell surface of mast cells and basophils by high-affinity receptors (FcγRI) for the Fc portion of the immunoglobulin. With repeated exposure, the antigen causes cross-linkage of two IgE molecules, and the cell is activated to release the anaphylaxis mediators: histamine, heparin, tryptase, kallikreins, proteases, proteoglycans, eosinophilic chemotactic factor of anaphylaxis, and neutrophil chemotactic factor of anaphylaxis.

Histamine and leukotrienes are potent vasoactive mediators, and their release from eosinophils and basophils increases vascular permeability and vasodilation. Hypovolemia then results from plasma leakage into the interstitial space. Histamine acts through H_1, H_2, and H_3 receptors to promote shock during allergen challenge. H_1 receptors mediate coronary vasoconstriction and cardiac depression, whereas H_2 receptors mediate gastric acid production and, when stimulated, produce coronary and systemic vasodilation and increases in heart rate and ventricular contractility. The H_1 receptor activation results in rhinitis, pruritus, and bronchoconstriction and stimulates endothelial cells to convert L-arginine into nitric oxide (NO), a potent vasodilator. Increased NO production decreases venous return. The resulting hypotension and hypoxemia/hypercapnia worsens the cardiovascular collapse.[3]

H_3 receptors have been identified on presynaptic terminals of sympathetic effector nerves that innervate the heart and systemic vasculature. These receptors inhibit endogenous norepinephrine release from sympathetic nerves, so activation accentuates the degree of shock observed during antigen challenge because compensatory neural adrenergic stimulation is blocked.[4]

Cross-linking of the FcγRI receptors also activates phospholipase A_2, setting off production of prostaglandins, thromboxanes, platelet activating factor, and leukotrienes. The protein kinases stimulate the synthesis of cytokines responsible for the late-phase inflammatory response. Cytotoxic events involving IgM or IgG, immune aggregates, activation of complement, kallikrein-kinin, or coagulation systems may also be involved in anaphylaxis. The systemic anaphylactic response is rapid; release of mediators from activated immune cells occurs within seconds to minutes, the arachidonic acid cascade is activated within minutes, and cytokine synthesis begins within hours.[5]

168.4 DIFFERENTIAL DIAGNOSIS

Anaphylaxis is a clinical diagnosis based on pattern recognition and probability. Systemic diseases that may result in clinical signs similar to those of anaphylaxis include severe asthma, pheochromocytoma, and mastocytosis. Inhalation of a foreign body can be misinterpreted as anaphylaxis.

168.5 CLINICAL MANIFESTATIONS

Anaphylaxis is a dynamic continuum, beginning with exposure to a trigger, followed by rapid onset, evolution, and resolution of clinical signs within minutes to hours.[6] There appears to be a correlation between the onset of signs and the severity of the reaction, with the more rapid the onset, the more severe the signs.[7] The clinical signs of anaphylaxis vary with the species and route of exposure. In dogs, hepatic signs predominate, with hepatic vein congestion and portal hypertension leading to vomiting and diarrhea. The reaction may progress to respiratory distress from upper airway obstruction, hypovolemic shock, and eventually death. Dermal reactions in dogs include generalized wheals, erythema, pruritus, and facial angioedema (Color Plate 168-1). Respiratory tract signs predominate in cats, with respiratory distress being the typical first sign of anaphylaxis. Dyspnea results from laryngeal and pharyngeal edema, bronchoconstriction, and excessive mucus production. Cats may also develop severe pruritus, vomiting, diarrhea, and hypovolemic shock that results in death.

The most severe clinical reactions of respiratory distress and cardiovascular collapse are generally seen when the antigen is administered parenterally. Oral ingestion of antigens more frequently causes GI distress and dermal reactions. Inhalation typically causes bronchoconstriction and rhinitis. Topical application of an antigen can cause conjunctivitis, urticaria, and pruritus, alone or along with systemic signs of anaphylaxis.

168.6 TREATMENT

168.6.1 Epinephrine

Epinephrine is the treatment of choice for anaphylaxis, but this is mostly on the basis of anecdotal experience (Table 168-1). Spontaneous recovery can occur in individuals because of compensatory mechanisms from endogenous epinephrine release and angiotensin II secretion. The rationale for using epinephrine is that stimulation of β-adrenergic receptors enhances the production of adenylcyclase and the subsequent conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (AMP). The cyclic adenosine monophosphate system inhibits the antigen-induced release of histamine and other anaphylactic mediators.

Efficacy was supposed from in vitro studies in which epinephrine inhibited mediator release from mast cells when administered before an allergen challenge. But in human patients with anaphylaxis and hypotension, standard therapy with intravenous epinephrine and fluids did not reverse the hemodynamic abnormalities.[8] Patients had a gradual recovery from hypotension that was not attributable to any specific therapeutic intervention.

In a canine ragweed anaphylactic shock model, epinephrine was effective in attenuating the circulatory collapse only when given by continuous intravenous infusion.[9] When administered as a bolus by the intravenous, intramuscular or subcutaneous routes, there was no sustained effect on hemodynamic recovery. In this model, endogenous plasma epinephrine concentrations increased from 500 pg/ml at baseline to 4000 pg/ml after antigen challenge. Even with this massive endogenous response, epinephrine concentrations were insufficient to reverse the cardiovascular collapse seen with antigen challenge.

As assessed by the area under the plasma concentration versus time curve, plasma epinephrine concentrations were significantly higher with epinephrine treatment by any route, but only with bolus administration was there a transient improvement in mean arterial pressure, stroke volume, and pulmonary wedge pressure. The improvement in mean arterial pressure was attributed to the increase in cardiac output from epinephrine's β-adrenergic effects on the heart and not to its α_1-vasoconstrictive effects on the systemic vasculature. Results of 728 the canine ragweed model suggest that in the treatment of anaphylaxis, once the mediators have been released 729 epinephrine acts primarily as a vasopressor in augmenting hemodynamic recovery and has no special pharmacologic properties that improve immunologic recovery.[3]

Table 168-1 Suggested Therapy for Anaphylaxis

Drug	Dosage and Route	Comments
Epinephrine	0.05 μg/kg/min IV via CRI 2.5 to 5 μg/kg IV 10 μg/kg IM	—
Atropine	0.02 to 0.04 mg/kg IV	—
Glucagon	1 to 2 mg (human dose) or 5 to 15 μg/min IV	For patients on β-blockers or that are unresponsive to epinephrine
Albuterol via inhalation	90 μg/actuation	Repeat as needed for bronchodilation
Ipratropium via inhalation	18 μg/actuation	For patients on β-blockers, repeat as needed for bronchodilation
Diphenhydramine	0.5 to 1 mg/kg IV, IM, or PO	—
Ranitidine	0.5 to 2.5 mg/kg IV or PO	—
Methylprednisolone sodium succinate	30 mg/kg IV	—
Dexamethasone	1 to 2 mg/kg IV	—
Crystalloid fluids	90 ml/kg/hr IV (dogs) 60 ml/kg/hr IV (cats)	Tailored to the individual patient
Dextran or hydroxyethyl starch (Hetastarch)	10 ml/kg/hr IV (dogs) 6 ml/kg/hr IV (cats)	For a total of 1 to 2 hr
Dopamine	5 to 10 μg/kg/min IV via CRI	Rate titrated to achieve adequate blood pressure

CRI, Constant rate infusion; *IM,* intramuscular; *IV,* intravenous; *PO,* per os.

From this canine model, it appears that a constant rate infusion (CRI) of epinephrine is the most effective treatment of cardiovascular collapse in an animal already in full anaphylactic shock. Epinephrine is supplied as human or veterinary formulations containing either 0.1 mg/ml (1:10,000) or 1 mg/ml (1:1000). Although ineffective for treatment of cardiovascular collapse, single intravenous or intramuscular boluses may be beneficial for bronchoconstriction and laryngeal edema. When given intramuscularly, epinephrine may be helpful in reversing mild hypotension, but the subcutaneous route should be avoided.

Common, transient side effects of epinephrine include pallor, tremor, anxiety, and palpitations. These correlate with its pharmacologic activity and are not a cause for concern. Rapid administration of inappropriately high concentrations of epinephrine can cause myocardial ischemia, which worsens cardiac dysfunction.[7]

168.6.2 Other Vasopressors

Human patients receiving β-blockers have an increased incidence and severity of anaphylaxis and can develop a paradoxical reaction to epinephrine. In these patients, intramuscularly or intravenously administered glucagon is suggested. Glucagon has inotropic, chronotropic, and vasoactive effects that are independent of β-receptors and causes endogenous catecholamine release.[10] Dopamine may be administered as a CRI for patients with refractory hypotension. Atropine may be administered if bradycardia persists despite the appropriate administration of epinephrine.

168.6.3 Antihistamines

Similar to the results seen with epinephrine, even pretreatment with histamine H_1 (chlorpheniramine maleate) or H_2 (ranitidine) blockers, an NSAID (indomethacin), or a lipoxygenase inhibitor did not prevent cardiovascular collapse in the canine anaphylactic shock mode. But pretreatment of dogs with the experimental H_3 receptor antagonist thioperamide maleate increased heart rate and improved left ventricular systolic function.[4,11] So although not very useful during the acute phases of anaphylaxis, H_1 and H_2 blockers frequently are administered to reduce pruritus and gastric acid secretion.

168.6.4 Glucocorticoids

Rapid-acting glucocorticoids are often administered in acute anaphylaxis, but beneficial effects are not seen for at least 4 to 6 hours. Glucocorticoids block the arachidonic acid cascade and may reduce the severity of late-phase reaction. Despite widespread use for treatment of asthma and allergic reactions, glucocorticoids themselves may cause allergic reactions and even anaphylaxis.[12] Because of a strong possibility of cross-reactivity between hydrocortisone, methylprednisolone, and prednisone, any formulation (succinate, acetate, or sodium phosphate) containing these glucocorticoids should be avoided in patients with allergic reactions to systemic steroids. Dexamethasone has been suggested as an alternative in such patients.

168.6.5 Fluid Therapy

Aggressive fluid resuscitation should be carried out in patients with hypotension. Administer isotonic crystalloids (e.g., normal saline) starting with shock bolus rates. Severely affected patients may require colloids 729
and vasopressor agents such as dopamine. Fluid therapy should be guided by heart rate, blood pressure, mucous 730
membrane color, capillary refill time, and respiratory rate and effort.

168.6.6 Ancillary Patient Treatment

During the early stages of respiratory distress, inhaled bronchodilators will have the fastest onset of action. Albuterol (salbutamol) is a β_2-adrenergic agonist bronchodilator and ipratropium bromide is a topical anticholinergic agent; both are available in metered dose inhalers. Early elective intubation is recommended in patients with stridor, lingual edema, or laryngeal or oropharyngeal swelling. If delayed, endotracheal intubation may be impossible and a tracheotomy must be performed. Oxygen should be administered as needed by nasal catheter or oxygen cage.

Patients that respond to therapy require careful observation, but there is no consensus on the observation time needed. Signs can recur in some patients (biphasic response). In humans, this typically occurs in 1 to 8 hours but has been reported to occur as long as 72 hours after the initial reaction. Avoidance of triggers for anaphylaxis is important, so a careful medical history is important to identify risk factors. Penicillin reactions are the most common antimicrobial-associated reactions documented in veterinary patients. Although this causes concerns regarding the use of cephalosporins in dogs and cats with previous reactions to penicillins, the incidence of cross-reactivity is actually low and a review concluded that it is safe to administer cephalosporins to penicillin-allergic humans.[13]

168.7 SUGGESTED FURTHER READING*

SF Kemp, RF Lockey: Anaphylaxis: A review of causes and mechanisms. *J Allergy Clin Immunol*. **110**, 2002, 341, *Review that discusses the pathophysiologic mechanisms of anaphylaxis, its causes, and its treatment*.

S Sell: Immunopathology. In RR Rich, TA Fleisher, TA Schwartz, et al. (Eds.): *Clinical immunology: Principles and practice*. 1996, Mosby, St Louis, *A review of the immunologic mechanisms of anaphylaxis*.

* See the CD-ROM for a complete list of references

169 Chapter 169 Drowning And Submersion Injury

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169.1 KEY POINTS

- Drowning, or submersion injury, is a leading cause of morbidity and mortality in human patients.
- Reports of drowning or near-drowning injury in veterinary patients are sparse.
- The primary pathophysiologic abnormality seen in near-drowning victims is hypoxic tissue damage due to the inability to inspire oxygen and expire carbon dioxide.
- The goals of therapy include neuroprotective therapy, cardiovascular support, and an oxygen-rich environment.
- Prognosis in humans depends on submersion time, cardiopulmonary resuscitation time, and severity of acidemia.

169.2 DEFINITIONS

Drowning accounts for more than 500,000 human deaths annually, worldwide. This number is thought to be grossly underestimated, primarily due to underreporting in less developed countries. Catastrophic natural disasters such as tsunamis, hurricanes, and floods add to the number of injuries and deaths attributable to drowning and near-drowning events. In the United States, in 2002, drowning accounted for 775 deaths in children ages 1 to 14 years, representing the second leading cause of death for this age group.[1] Because of the high incidence of drowning and near-drowning injury, a consensus conference was held to establish guidelines for uniform reporting of data from drowning incidents and to stratify definitions for drowning and its associated pathologic complications.[2] In addition, a systematic review of 43 articles addressing the definition of drowning found 33 different definitions describing drowning incidents: 20 for drowning and 13 for near drowning.[3]

The Consensus Conference on Drowning published its recommended guidelines for uniform reporting of data from drowning in 2003.[2] The following definitions were presented from the consensus conference for use in research and data reporting when associated with drowning and near-drowning victims:

- Drowning is a process resulting in primary respiratory impairment from submersion or immersion in a liquid medium. Liquid is present at the victim's airway, preventing respiration of air. The victim may survive or die, but regardless of outcome, the victim has been involved in a drowning incident. This is in contrast to the definition proposed by the American Heart Association in 2000, reserving the term *drowning* for victims who die from water submersion within 24 hours of the event.[4]
- *Dry drowning* describes victims who do not aspirate liquid into the lungs, whereas *wet drowning* refers to aspiration of liquid. Victims of dry drowning often experience morbidity from laryngospasm, resulting in the same hypoxemic and hypercarbic state seen in those that have aspirated liquid.

- It was concluded in the consensus statement that *near drowning* be abandoned as a term used to describe victims of submersion injury that ultimately survive, because the term *drowning* is inclusive of both survivors and nonsurvivors. The term *submersion victim* was proposed as an alternative to *near-drowning victim* by the American Heart Association and still is in use.

169.3 INCIDENCE AND EPIDEMIOLOGY

169.3.1 Humans

The incidence of drowning and submersion injury remains high in humans. Drowning is the third most common cause of accidental death in humans younger than 44 years of age, with 40% of all drowning deaths reported in children less than 5 years of age.[5] Another 15% to 20% of drowning victims are between the ages of 5 and 20 years, and male victims dominate in all age-groups.[5] Most drownings occur in fresh water, with children younger than 1 year of age most often drowning in bathtubs, buckets, or toilets.[6] Drowning most often occurs in residential swimming pools in children aged 1 to 4 years.[7,8] In contrast, adolescents most often drown in rivers, lakes, and canals, and drug or alcohol use is a contributing factor in about 50% of these cases.[9,10] Male individuals are thought to have a higher incidence of drowning, especially during adolescence, because of the tendency toward risky activities and overestimation of their swimming abilities.[11]

Factors associated with a higher risk of drowning in humans include the use of alcohol or recreational drugs, lack of supervision in children, and medical conditions such as epilepsy and long QT syndrome.[12,13]

169.3.2 Veterinary Patients

There are only two published reports of veterinary patients involved in drowning incident. The first is a case report of a gelding that recovered from a drowning incident in which he became entangled in a safety line attached to his harness while swimming in a chlorinated swimming pool. The reported adverse effects of the incident included metabolic acidosis, hypoxemia, and pulmonary infiltrates in the dorsocaudal lung fields. Successful therapy included antibiotics and bronchoalveolar lavage with surfactant.[14]

The second publication referring to drowning in veterinary patients describes animal abuse cases in a population of dogs and cats in the United Kingdom. In this sample of 243 dogs and 182 cats, drowning accounted for 3 of the feline abuse cases.[15] Anecdotally, a drowning canine victim survived with high morbidity, developing secondary pneumonia (transtracheal fluid wash positive for *Staphylococcus intermedius*) and requiring a 7-day intensive care hospital stay with oxygen support.

The pathophysiology and clinical course of veterinary patients involved in drowning incidents probably correlates well with the human progression of injury, directing diagnostics, therapy, and outcome in canine and feline drowning victims.

169.4 PATHOPHYSIOLOGY OF INJURY

169.4.1 Pulmonary

Drowning occurs without aspiration of water in about 10% of victims, whereas 90% aspirate fluid into the lungs.[16] All submersion victims experience hypoxemia, either from laryngospasm in which no aspiration occurs or aspiration of fluid resulting in loss of surfactant causing atelectasis and intrapulmonary shunt. Most (about 85%) submersion victims that survive are thought to have aspirated less than 22 ml/kg of water.[16]

Hypoxemia in submersion victims results from intrapulmonary shunting of blood. Bronchospasm, atelectasis due to surfactant washout, aspirated water or matter in the alveolar space, infectious or chemical pneumonitis, and acute respiratory distress syndrome (ARDS) all contribute to this shunting in submersion victims.[17] An intrapulmonary shunt is defined as a portion of the cardiac output that enters the left side of the heart without being oxygenated in the lungs as a result of pathology of the lung parenchyma.[18] There are three different types of intrapulmonary shunts: anatomic shunts, capillary shunts, and venous admixture.

Submersion victims may experience both the capillary and venous admixture types of shunting. Capillary shunts describe blood that passes through the lungs but does not get oxygenated because it does not respire with alveolar gas. In submersion victims that aspirate water into the alveolar space, surfactant washout causes atelectasis, resulting in capillary shunting. Venous admixture occurs when blood traverses the pulmonary capillaries and respires with alveoli that have low oxygen tension. This occurs primarily because of ventilation-perfusion inequality, which may be present in submersion victims that aspirate water or particulate matter.

169.4.2 Fluids and Electrolytes

In previous years, medical researchers tried to ascertain the differences in pathology when drowning victims aspirated fresh versus salt water. It was thought that the hypertonicity of aspirated salt water would result in an osmotic gradient into the lungs, drawing plasma water into the pulmonary interstitium and alveolar spaces. This shift of plasma water would then result in hypernatremia and a decreased circulating blood volume. In contrast, aspiration of fresh water was hypothesized to shift fluid out of the lung and into circulation, resulting in hypervolemia, hyponatremia, and dilution of other electrolytes.

Studies did not support these hypotheses. One experimental study showed that the amount of aspirated water needed to cause these fluid shifts were far greater than the amount normally aspirated by drowning victims.[19] In another study evaluating a series of 91 submersion victims, no serious fluid or electrolyte abnormalities were noted.[20] The most prominent pathology in victims of both fresh and salt water submersion injury continues to be the washout of surfactant from the alveoli, causing atelectasis, intrapulmonary shunt, and global hypoxia, which may then result in tissue injury, neurologic damage, cardiovascular collapse, and death.

169.4.3 Neurologic and Cardiovascular

In humans, about 10% of drowning victims experience severe neurologic outcomes.[21] Neurologic abnormalities 731 732 are a result of hypoxia-induced brain injury, and the severity of injury is primarily dependent on the duration of hypoxia.

Cardiac arrhythmias and dysfunction may occur in submersion victims as a result of myocardial hypoxia and ischemia, acidemia, electrolyte abnormalities, and hypothermia. Blood pressure is affected by a variety of factors, including catecholamine release, hypercarbia, and hypovolemia from traumatic blood lost during the submersion event. Hypothermia may contribute to hypovolemia caused by inhibition of antidiuretic hormone and induction of diuresis, which results from shunting of blood to core organs, giving a perception of hypervolemia via arterial stretch receptors.[17]

169.4.4 Effect of Water Temperature

Water temperature has an important effect on the survivability of submersion victims. Submersion in ice-cold water (<5° C) increases the chances of survival, in part because of the diving reflex that is present in most mammals. Within seconds of a victim's face contacting cold water and before unconsciousness ensues, a reflex mediated by the trigeminal nerve sends impulses to the central nervous system, causing bradycardia, hypertension, and preferential shunting of blood to the cerebral and coronary circulations.[5,22] This reflex acts to protect the brain and heart from hypoxia-induced injury. Hypothermia also causes a decrease in metabolic need, protecting the brain from injury. The effects of this response are evidenced by good neurologic recovery in victims submerged in icy water, despite the initial presence of coma or other negative neurologic prognostic indicators. Hypothermia in patients with submersion injury in warm water, however, is a negative prognostic sign, indicating poor peripheral perfusion and longer submersion times.[5]

169.5 DIAGNOSTIC TESTS AND MONITORING

On presentation at a hospital, airway, breathing, and circulation should be assessed immediately in the submersion victim. Body temperature should be evaluated and treated appropriately. In patients with significant neurologic impairment, therapeutic hypothermia may be beneficial in protecting the brain from further injury.[23] A minimum database, including complete blood count and chemistry profile, should be collected. Arterial blood gas analysis should be performed, because many submersion victims experience hypoxemia, respiratory acidosis from hypoventilation, and metabolic acidosis from hypoperfusion and tissue hypoxia.

Monitoring of the near-drowning victim includes continuous electrocardiogram, respiratory rate and effort, lung auscultation, body temperature, mentation and pupil responsiveness, arterial blood pressure, serum electrolytes, and arterial blood gas analysis. Continuous pulse oximetry can be used to monitor hemoglobin saturation. Thoracic radiography should be performed when the patient is able to tolerate the procedure.

169.6 TREATMENT

Most human submersion victims are pulled from the water and cardiopulmonary resuscitation is attempted at the scene. Cardiopulmonary resuscitation in canine or feline patients at the scene of the accident is much more difficult without proper training. The owner should wrap the pet in a blanket, perform mouth-to-nose breathing if no respirations are noted, and present the animal to an emergency clinic as quickly as possible.

Therapy of the drowning victim is aimed at improving tissue oxygenation, resolving abnormal serum acid-base status, maintaining tissue perfusion, and stabilizing the cardiovascular and neurologic systems. Hypoxemia and respiratory and metabolic acidosis should be treated as early and aggressively as possible to prevent further organ damage. Oxygen should be administered and, if indicated, the patient should be intubated and artificially ventilated. Guidelines used in human medicine to indicate the need for intubation and assisted ventilation include an arterial partial pressure of oxygen (PaO_2) of less than 60 mm Hg, an oxygen saturation of less than 90%, or worsening hypercapnia.[5] These guidelines may be broadened in veterinary patients according to the skill and finances necessary to manage a ventilator patient (see Chapter 213, Basic Mechanical Ventilation).

Pulmonary dysfunction occurring as a result of submersion injury may progress to pneumonia or acute respiratory distress syndrome (ARDS). In humans, ARDS is defined by the clinical presentation of four factors: (1) acute respiratory distress, (2) bilateral pulmonary infiltrates, (3) a PaO_2-to-fraction of inspired oxygen ratio of less than 200, and (4) a pulmonary artery wedge pressure less than 18 mm Hg or no evidence of left atrial hypertension.[24] These patients often require positive end-expiratory pressure (PEEP) to decrease pulmonary shunt, improve blood oxygenation, and increase lung compliance in atelectatic areas. PEEP is provided through intubation and mechanical ventilation.

Artificial surfactant has been used with some success, and experimental therapies with liquid ventilation, inhaled nitric oxide, and intratracheal ventilation may be employed.[25-28] Lastly, submersion victims are prone to develop pneumonia, especially if the submersion medium was grossly contaminated or aspiration of dirt or sand occurred. Antibiotic therapy ideally should be instituted following a culture of bronchoalveolar (BAL) fluid obtained with a tracheal wash or AL. However, in unstable patients, prophylactic use of a broad-spectrum antibiotic may be indicated.

Fluid therapy is necessary in drowning victims to restore circulating volume, correct acid-base abnormalities, and improve tissue perfusion. However, excessive crystalloid administration may worsen noncardiogenic pulmonary edema and cerebral edema. Colloid therapy used in conjunction with crystalloids can help maintain intravascular volume and decrease the risk of extravasation of excess fluid into interstitial tissue spaces. Fluid therapy should be monitored with serial body weights, central venous pressure values, urine output, and arterial blood pressure measurements.

Neurologic resuscitation is aimed at preventing or decreasing cerebral edema and maintaining normal intracranial pressures. Elevations in $PaCO_2$ levels cause cerebral vasodilation, contributing to an increase in intracranial pressure and promoting the potential for cerebral edema. It is recommended to maintain normocapnia, because hyperventilation to cause hypocapnia may result in cerebral vasoconstriction and impair cerebral perfusion. Hypertonic therapy such as mannitol may be used in fluid-resuscitated patients if cerebral edema is suspected and neurologic status is deteriorating. Glucocorticoid therapy is not recommended, because it has not been shown to improve neurologic outcome, and the resultant hyperglycemia may worsen cerebral cell damage through secondary neuronal injury.[29]

169.7 OUTCOME

In one study, three factors were associated with 100% mortality in human submersion victims younger than 20 years of age: (1) submersion duration greater than 25 minutes, (2) resuscitation duration longer than 25 minutes, and (3) pulseless cardiac arrest on presentation at the emergency department.[30] Additional factors associated with a poor prognosis included ventricular tachycardia or ventricular fibrillation (93% mortality), fixed pupils (89% mortality), severe acidosis (89% mortality), and respiratory arrest in the emergency department (89% mortality).[30] Patients experiencing acute pulmonary edema had mortality rates ranging from 5% to 19%. Level of consciousness and responsiveness also correlated with survival. Deaths occurred only among victims who remained comatose after presentation to the emergency department. No deaths occurred in patients who arrived alert or depressed but responsive.[31]

Outcome is not known in veterinary patients with drowning injury because of the lack of reporting in the veterinary literature. Correlation with prognosis in human submersion victims may be made, although in many instances submersion duration may not be known and prehospital therapy, including cardiopulmonary resuscitation, is usually not performed.

Drowning victims with minimal neurologic, respiratory, and cardiovascular abnormalities should have better outcomes; however, intensive therapy of more affected submersion victims can result in a full recovery. The ability to provide adequate inspired oxygen levels, to provide mechanical ventilation if needed, to evaluate serial arterial blood gases, and to house the patient in a 24-hour intensive care setting may improve the prognosis in severely affected patients.

169.8 SUGGESTED FURTHER READING*

AE Burford, LM Ryan, BJ Stone, et al.: Drowning and near-drowning in children and adolescents: a succinct review for emergency physicians and nurses. *Pediatr Emerg Care*. **21**, 2005, 610, *An excellent review of drowning and near-drowning, including statistics and guidelines for therapy*.

LK DeNicola, JL Falk, ME Swanson, et al.: Submersion injuries in children and adults. *Crit Care Clin*. **13**, 1997, 477, *An excellent review of drowning and submersion injuries in humans*.

A Gabrielli, AJ Layon: Drowning and near-drowning. *J Fla Med Assoc*. **84**, 1997, 452, *An updated review on drowning and near-drowning, addressing management modalities such as glucocorticoid therapy, among others*.

JH Modell: Drowning. *N Engl J Med*. **328**, 1993, 253, *This is a great, detailed review of drowning and submersion injury in humans*.

JH Modell, SA Graves, A Ketover: Clinical course of 91 consecutive near-drowning victims. *Chest*. **70**, 1976, 231, *Study evaluating electrolytes, blood gas analysis,* PaO_2*-to-fraction of inspired oxygen, survival based on neurologic signs on arrival, and overall survival in near-drowning victims*.

* See the CD-ROM for a complete list of references.

170 Chapter 170 Fat Embolism

Alan M. Klide, VMD, DACVA

170.1 KEY POINTS

- There are many causes of fat embolism, but it most commonly results from traumatic injuries, especially long-bone fractures.
- Fat embolism is often a diagnosis of exclusion.
- Fat embolism often is not considered a cause of morbidity and mortality in veterinary patients and is reported infrequently in animals.
- Fat embolism is easily and consistently created in dogs with procedures that mimic clinical orthopedic procedures.
- The vast majority of reports and investigations concern endogenous fat as the source of embolus, but there are a few reports of fat embolism from exogenous sources.
- Clinical signs of fat embolism may include right ventricular failure, cardiovascular collapse, hypoxemia, neurologic changes, fever, petechial rashes, tachycardia, retinal changes, renal failure, tachypnea, and dyspnea.
- Treatment of fat embolism is somewhat controversial and is mostly nonspecific and supportive.
- Pulmonary contusions combined with fat embolism produce a greater degree of pulmonary change than either alone.

170.2 INTRODUCTION

Fat embolism is a frequently overlooked but important subject in veterinary medicine. In human medicine, the detrimental effects of embolic fat have been recognized for almost 200 years.[1] Wars have provided much material and information.[1] There are many possible causes for its occurrence, and the fat sources have been studied but are not always clear. It has been said that fat embolism does not occur in animals or that it has not been reported in animals. Both of these statements are incorrect. Fat embolism can be a severe, life-threatening event that should be considered in the proper patients and circumstances.

170.3 DEFINITIONS

There are two definitions related to the subject.[2] The first is the term *fat embolism*. It usually is used to mean fat within the circulation that can produce embolic phenomena that may or may not lead to clinical sequelae. The second term is *fat embolism syndrome,* which refers to fat in the circulation that is associated with an identifiable pattern of clinical signs that typically occurs 24 to 72 hours after the event. It is a collection of respiratory, hematologic, neurologic, and cutaneous signs associated with trauma or other surgical and medical conditions.[2]

170.4 CAUSES

170.4.1 Predisposing Causes

The incidence of fat embolism is highest following trauma, especially lower limb fractures. However, it can be associated with many other conditions such as soft-tissue injury, liposuction, acute pancreatitis, burns, diabetes mellitus, joint reconstruction, cardiopulmonary bypass, and decompression sickness.[2-3]

When considering fat embolism as a rule-out, it should be remembered that the source of the fat may be exogenous or endogenous. The vast majority of the literature on the subject relates to endogenous sources of fat; however, there are a few reports regarding exogenous sources. These are related to relatively new drugs and techniques such as propofol,[2,4] total parenteral nutrition,[2,5] and transcatheter arterial chemoembolization with lipiodol.[6]

170.4.2 Actual Causes

The sources of the endogenous fat have been variously reported. Incriminated[1] factors include alterations of lipid metabolism, changes in the coagulation mechanisms that affect lipids, shock, or atraumatic perturbations in the physical state of the blood. Another possible cause is mechanical,[1] also called the *infloating theory,*[2] which states that the fat is physically forced into the venous system following trauma. Capillaries in bone are relatively wide compared with those in the systemic circulation. These capillaries empty into wide sinusoids that are supported by a fibrous network attached to the intramedullary trabeculae. After trauma, many of these sinusoids remain distended rather than collapsing as do veins in soft tissue. Rupture of these delicate structures and increased pressure can force marrow or fat, or both, into the sinusoids.[1] Intramedullary manipulations,[2] such as reaming and increased pressure (i.e., following cementing) have been shown to cause fat embolism as well.

Systemic embolization without pulmonary effects has been seen and is somewhat confusing.[2] The most commonly cited explanation is passage of the emboli through a patent foramen ovale,[2,7-9] but there are many reports of fat in the systemic circulation in patients without a patent foramen ovale.[2,8,10,11]

A possible biochemical mechanism is known as the *lipase theory:* elevated plasma lipase following trauma destabilizes circulating fats by demulsification, saponification, and mobilization of lipid stores.[2] Another, less 734
proven, biochemical mechanism is called the *free fatty acid theory,* in which circulating free fatty acids directly 735
damage pneumonocytes and create gas exchange abnormalities.[2]

There may be multiple mechanisms acting synergistically to cause fat embolism syndrome and perhaps also explain the delay in clinical signs. Trauma leads to catecholamine release, which promotes the release of free fatty acids.[12] Human patients with trauma or sepsis have elevated C-reactive protein levels that cause chylomicrons to coalesce and form fat globules.[13] Therefore factors related to lipid metabolism may provide a connection between the traumatic and atraumatic forms of the fat embolism syndrome. Interestingly, the mechanisms that cause acute respiratory distress syndrome (ARDS) in animals with severe pancreatitis may resemble those causing ARDS associated with fat embolism syndrome.

170.5 INCIDENCE

A review of the incidence of fat embolism in traumatized surgical patients and those undergoing elective orthopedic surgery[2] illustrates some conflicting results. The incidence of fat embolism in retrospective studies appears very low (<1%), and the frequency in prospective investigations is much higher (11% to 19%). Most postmortem analyses have shown much higher incidences, up to 60.4%.

170.6 DIAGNOSIS

Fat embolism syndrome is a collection of signs, many of which are common to other causes of critical illness, therefore making it a diagnosis of exclusion.

170.6.1 Clinical Signs

Signs may occur intraoperatively, but more commonly the onset is gradual, typically appearing 12 to 48 hours following injury.[2,14] Signs may include right ventricular failure, cardiovascular collapse, hypoxemia, neurologic manifestations (confusion, drowsiness, coma, stupor, rigidity, convulsions), fever, petechial rash, tachycardia, retinal changes (fat or petechiae), renal changes (anuria or oliguria), tachypnea, and dyspnea. Modern monitoring equipment such as transcranial Doppler imaging and transesophageal echocardiography may improve intrasurgical detection of fat embolism.[15,16]

170.6.2 Laboratory Tests

Most laboratory tests are nonspecific for fat embolism,[14] including increased serum lipase or phospholipase A_2 levels. Cytologic examination of urine, blood, and sputum with Sudan or oil red O staining may detect fat globules that are either free or in macrophages. Blood lipid levels are not helpful. Other changes include decreased hematocrit, thrombocytopenia, and alterations in coagulation.

170.7 CASES IN HUMANS

Some human cases are referenced here[6-10,17-23] for several reasons: they demonstrate what is in the literature, they demonstrate a range of effects in patients, and they are a source for further information on the subject and for some of the papers that address questions of surgical technique in relation to the incidence of fat embolism syndrome. These cases all represent endogenous fat sources and, as stated before, they are the vast majority of cases, but also include a few reports of exogenous causes.[2,4-6]

170.8 ANIMAL REPORTS

170.8.1 Experimental Reports

These experimental animal studies and reports were done to investigate various questions relating to fat embolism in humans. They are included here not only for that reason but to demonstrate that fat embolism can be caused in animals at all, and further that it can consistently be caused by techniques that replicate clinical veterinary surgery. They are also presented to show some of the cardiopulmonary and other organ changes that may occur in dogs. They present information on the transit of fat from the venous circulation to the systemic arterial circulation in the absence of patent foramen ovale.

In the papers that will be cited here, fat embolism was caused in dogs by the following methods:

- Drilling and reaming the femoral medullary canal followed by placement of bone cement and followed by hammering metal rods into the medullary cavities[11]
- Femoral and tibial reaming followed by pressurization of the intramedullary canal by placement of methylmethacrylate cement and insertion of a contoured Steinmann pin[22]
- Cemented arthroplasty[16]
- Femoral and tibial reaming followed by pressurization of the intramedullary canal by placement of methylmethacrylate cement and insertion of a contoured Steinmann pin, followed in the experimental groups by creation of a femoral fracture by notching the lateral cortex of the femur with a saw and then applying a three-point bending jig to the lateral aspect of the femur to create a standard transverse fracture in the middle of the femoral shaft[25]
- Reaming of the femoral intramedullary cavity followed by placement of methylmethacrylate and then followed by a stainless steel rod simulating a prosthesis[26]

Summary of changes found in one of these studies[11] in dogs, are as follows:

- Pulmonary artery pressure goes up after embolizations, approximately doubling.
- Intravascular fat was found in all brain, heart, and kidney specimens examined.
- No patent foramen ovale was found in any dogs examined.
- Fat globules can traverse the pulmonary circulation.
- There was no evidence of acute inflammation around fat-occluded pulmonary vessels.

170.8.1.1 Summary

A summary of the results of studies of pulmonary contusion and fat embolism in dogs[24] is that the combination of pulmonary contusion and fat embolism leads to more substantial pulmonary dysfunction than does either alone. This includes decreased partial pressure of arterial oxygen, decreased ratio of partial pressure of arterial oxygen to the fractional inspired oxygen concentration, a significant increase in peak airway pressure, an increase in the alveolar-arterial oxygen gradient and pulmonary artery pressure that lasted for 5 hours, decreased total thoracic compliance, an increased percentage of the glomerular and cerebral areas occupied by fat, and decreased systolic blood pressure.

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170.8.2 Clinical Cases

There are a few clinical reports of fat embolism in dogs[27,28] and a cat.[29]

One of the reports is about two dogs.[27] One dog was hit by a car and had a fractured femur. It was repaired with a plate and screws. The dog was sent home after 3 days. Two days later the dog was found dead by the owner. The pathologic diagnosis was fractured femur and fat embolism of the brain.

The second dog was hit by a car. It suffered an inguinal hernia and multiple pelvic fractures and a femoral fracture. The inguinal hernia was repaired, and then 4 days later surgery was performed to stabilize the right hemipelvis and to repair the femoral fracture. On the third postoperative day the dog was bright and alert with normal temperature, pulse, and respirations. It was found dead 10 to 15 minutes later. The pathologic diagnosis was fracture of the pelvic bones, cardiac infarction, pulmonary fat embolism (occluding most of the middle-sized arteries of the lungs), and renal glomerular fat embolism.

Another report[28] was of a dog that received a unilateral cemented total hip arthroplasty. The acetabular component was implanted. After preparation of the femoral canal, polymethylmethacrylate was packed into the femoral medullary cavity. As the femoral prosthesis was being impacted, the dog's expired carbon dioxide decreased from 40 mm Hg to about 20 mm Hg. This was followed by sinus bradycardia. The arterial oxygen saturation decreased to less than 90%, and ventricular asystole followed. Resuscitation efforts were started, and normal sinus rhythm resumed. Ventricular asystole occurred again after 1 minute. After 25 minutes of attempted cardiopulmonary resuscitation, the efforts were stopped. Microscopic examination of hematoxylin and eosin-stained, formalin-fixed, and oil red O-stained, frozen tissue sections confirmed the presence of large numbers of fat globules in blood vessels in the lungs, liver, and kidneys.

There is one report about a cat.[29] The cat was hit by a car. It suffered a diaphragmatic hernia, multiple rib fractures, a fractured humerus, and a tibial fracture. The diaphragmatic hernia was repaired, and repair of the orthopedic injuries was postponed for 4 days. After 15 minutes of surgery, while the surgeon was advancing an intramedullary pin within the humerus, the output from the Doppler monitor was lost, respiratory arrest was diagnosed; heart sounds were heard, but there were no palpable pulses. Cardiopulmonary resuscitation was begun and continued for 20 minutes, but to no avail. Tissue sections embedded in gelatin were cut with a freezing microtome and stained with oil red O and Mayer's haemalum. This confirmed that the vacuoles seen were fat emboli. They were quantified and the counts were in the range of severe fat embolism.

170.9 TREATMENT

Treatment is nonspecific and supportive. Because of difficulties in diagnosis and the small numbers of patients studied (either small numbers in a group or individual patients), the results are difficult to interpret.[2] Early resuscitation and stabilization seem to be of major importance. The most common manifestations of fat embolism syndrome are pulmonary, so any patient at risk should be monitored closely and provided with pulmonary care as needed.

Corticosteroids have been studied extensively in the treatment of fat embolism in animals and humans. Many of the results are positive, but there are also considerable negative findings. Similarly the use of heparin is contradictory. Glucose has been used as a prophylactic strategy. Alcohol decreases serum lipase activity, and the incidence of fat embolism syndrome is less common in accident victims whose blood alcohol levels were greater than 0.3 g/dl. Aspirin has been recommended as a prophylactic agent. There is a report of using percutaneous cardiopulmonary support in a case of catastrophic massive pulmonary fat embolism.[30]

170.10 SUGGESTED FURTHER READING*

RJ Byrick, JB Mullen, CD Mazer, et al.: Transpulmonary systemic fat embolism: Studies in mongrel dogs after cemented arthroplasty. *Am J Respir Crit Care Med*. **150**, 1994, 1416, *An excellent study and article examining fat embolism after cemented arthroplasty in dogs*.

M el-Ebiary, A Torres, J Ramirez, et al.: Lipid deposition during the long-term infusion of propofol. *Crit Care Med*. **23**, 1995, 1928, *An article that describes how propofol can serve as a source of fat embolization*.

AW Elmaraghy, S Aksenov, RJ Byrick, et al.: Pathophysiological effect of fat embolism in a canine model of pulmonary contusion. *J Bone Joint Surg [Am]*. **81**, 1999, 1155, *An excellent article that looks at the cardiopulmonary effects of pulmonary contusion, fat embolism, and a combination of pulmonary contusion and fat embolism in a canine model*.

A Mellor, N Soni: Fat embolism. *Anaesthesia*. **56**, 2001, 145, *A good, up-to-date review article*.

T Schwarz, PE Crawford, MR Owen, et al.: Fatal pulmonary fat embolism during humeral fracture repair in a cat. *J Small Anim Pract*. **42**, 2001, 195, *A report of fatal pulmonary fat embolism during humeral fracture repair in a cat*.

* See the CD-ROM for a complete list of references.

171 Chapter 171 Tumor Lysis Syndrome

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171.1 KEY POINTS

- Tumor lysis syndrome (TLS) is a rare but potentially fatal constellation of metabolic abnormalities in veterinary oncology patients.
- TLS is seen most commonly in patients with chemotherapy-responsive or radiation-responsive diseases, such as lymphoma or lymphoid leukemias, hours to a few days after treatment. Patients at highest risk include those with dehydration or advanced disease and with rapid induction of remission with treatment.
- The metabolic complications of TLS are due to rapid tumor cell death and are characterized by hyperphosphatemia, hyperkalemia, metabolic acidosis, and hypocalcemia, with or without azotemia. These metabolic abnormalities may be further exacerbated in patients with renal dysfunction.
- Clinical signs of TLS can include depression, vomiting or diarrhea, or both (many times hemorrhagic), bradycardia, and cardiovascular collapse culminating in shock.
- Rapid diagnosis and therapy for TLS is essential because mortality rates are high. Treatment for TLS is: (1) aggressive fluid therapy, (2) correction of acid-base and electrolyte abnormalities, and (3) discontinuation of chemotherapy or radiation until the patient is normal clinically and biochemical parameters are within normal limits.

171.2 INTRODUCTION

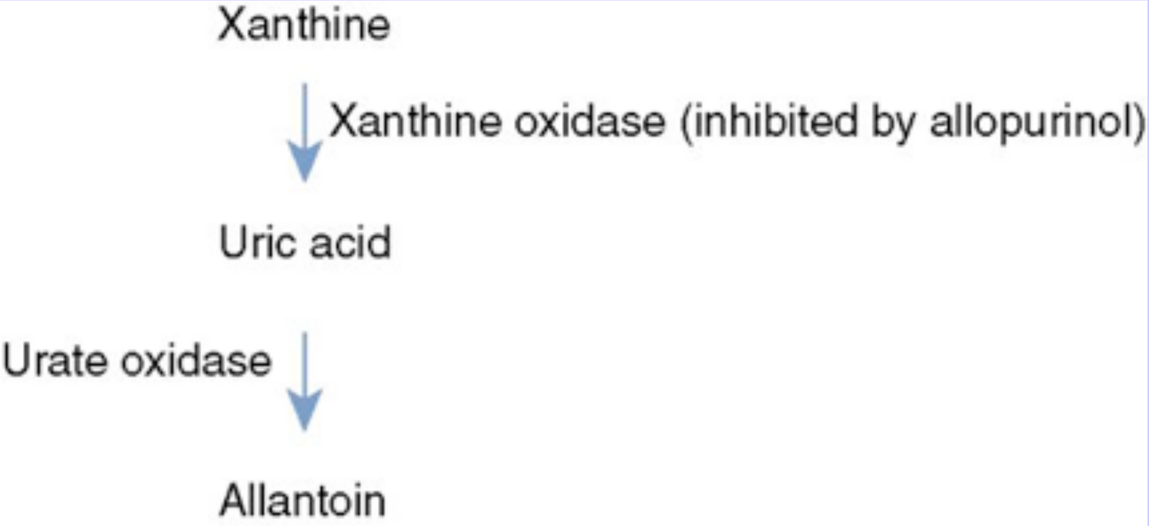
Tumor lysis syndrome (TLS) is a constellation of metabolic abnormalities that may be observed in veterinary oncology patients.[1,2] Clinically significant TLS is seen most often shortly after cancer treatment and is associated with significant morbidity and mortality.[2-4] The precise incidence of TLS is not defined in veterinary oncology, but is likely rare because only sporadic cases are reported.[5-7] The severity and nature of the metabolic alterations are often variable depending on the timing and intensity of therapy, the enormity of tumor lysis, and the hydration and renal status of the patient. The risk factors, pathogenesis, metabolic complications, and therapeutic strategies of TLS are discussed in this chapter.

171.3 RISK FACTORS

TLS is seen most commonly in veterinary patients with chemotherapy-responsive and radiation-responsive diseases, such as lymphoma or lymphoid leukemias. TLS usually is noted within a short time after treatment, typically hours to a few days, but onset can be as long as 5 to 7 days after treatment.[5] Patients at highest risk include those with dehydration or advanced disease and with rapid induction of remission after treatment.[5-7]

The dose-response curves for most cytotoxic chemotherapy agents are sigmoidal in shape, suggesting that small reductions in dosage can translate into large reductions in efficacy.[8] Given that TLS is a rare syndrome in veterinary patients, this author does not recommend routine dosage reduction or changes in protocol schedules to prevent TLS unless the patient has all of the aforementioned risk factors.

Figure 171-1 Diagram of the purine catabolism pathway.



171.4 PATHOGENESIS AND METABOLIC COMPLICATIONS

The pathogenesis of TLS is related to rapid tumor cell destruction, which may result in release of intracellular ions and metabolic byproducts into the extracellular environment and systemic circulation. The metabolic complications of TLS are therefore characterized by hyperphosphatemia, hyperkalemia, and metabolic acidosis with or without azotemia.[1,5] The hyperphosphatemia can secondarily induce hypocalcemia.

Acute renal failure is a common sequela of TLS and the pathophysiology is likely multifactorial.[9] Not only do hyperphosphatemia and hyperuricemia result from TLS, they also contribute to the oliguric acute renal failure in these patients. Causes may include tubular precipitation of calcium phosphate and nucleic acid metabolites (and secondary intraluminal tubular obstruction), intravascular volume depletion, and poorly understood malignancy-associated nephrotoxins. A diagram of the purine metabolism pathway is shown in Figure 171-1 and is discussed further in the Treatment section.

171.5 CLINICAL SIGNS AND DIAGNOSIS

The most common clinical signs of TLS are depression and vomiting or diarrhea, or both (many times hemorrhagic). Additional clinical signs may include bradycardia and other arrhythmias secondary to hypocalcemia, and pale mucous membranes and prolonged capillary refill time due to decreased cardiac output from hypodynamic shock.

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When these clinical signs and the aforementioned metabolic abnormalities are present with a history of relatively recent chemotherapy or radiation therapy in a patient with lymphoma, lymphoid leukemia, or other extremely therapy-responsive neoplasia, the diagnosis of TLS can be made. It is important to note that some of these clinical signs can be seen in other oncology patients suffering from neutropenia, coagulopathies, sepsis, or multiple organ failure. Therefore a complete physical examination and history are paramount, as are a hemogram, biochemical profile, urinalysis, and possibly other diagnostics, such as radiographs and blood or urine cultures, depending on the results of the previous diagnostic tests.

171.6 TREATMENT

Once a diagnosis of TLS is made, the mainstays of therapy are restoration of tissue perfusion with aggressive administration of fluids and stabilization of the cardiovascular system in severely affected patients. Secondary end points for therapy will then also include the correction of electrolyte and acid-base disturbances and renal indexes.

In severely affected patients, one should treat for shock as outlined in Chapters 10 and 65, Shock and Shock Fluids and Fluid Challenge, respectively. Normal saline may be the best crystalloid for fluid administration in TLS until the hyperphosphatemia and hyperkalemia are corrected. Fluid rates will depend on the severity of compromise; however, doses of 50 to 90 ml/kg of crystalloids may be necessary initially to treat acute shock states. Subsequent fluid rates are typically reduced to 5 to 10 ml/kg/hr, with close patient monitoring for further rate changes as necessary. Hypocalcemia secondary to hyperphosphatemia should be treated with parenteral calcium supplementation only in patients with significant clinical signs of hypocalcemia. Additional chemotherapy or radiation therapy should be withheld until the patient has fully recovered.

Additional therapeutic measures that are used more commonly in human TLS cases include urinary alkalinization and administration of allopurinol or urate oxidases (see Figure 171-1). These additional treatments are not recommended routinely for veterinary patients with TLS for a variety of reasons. First, although hyperuricemia occurs in veterinary TLS cases, it is not typically as significant an inducer of subsequent renal problems in veterinary species as it is in humans because of differences in endogenous urate oxidase distribution and efficacy across species.[5,10] Second, as further discussed in the Comparative Aspects section that follows, urate oxidase therapies are specific for humans, can precipitate allergic reactions in humans, and have not been evaluated in veterinary species. Lastly, urinary alkalinization should be performed only when hyperuricemia is present in humans, and although allopurinol and alkalinization reduce the risk of uric acid precipitation, they increase the risk for precipitation of urinary xanthine and calcium phosphate crystals, respectively.[11]

171.7 COMPARATIVE ASPECTS

The incidence of TLS in humans is reported to be as low as 0.5% and as high as 28%.[12,13] The incidence varies greatly depending on numerous risk factors including tumor type (highest risk in lymphomas, lymphoid leukemias, and small cell lung cancer), chemotherapy protocol, advanced stage, increased lactate dehydrogenase levels, increased pretreatment uric acid levels and poor renal function, and the presence of effusions.[14,15] Neither racial nor gender predilection exists.

The mainstays of human TLS therapy include aggressive fluid supplementation, as outlined in the Treatment section. Although urinary alkalinization is performed much more commonly in human TLS therapy, urinary alkalinization should be performed only when hyperuricemia is present. Similarly, although alkalinization and allopurinol reduce the risk of uric acid precipitation, they increase the risk for formation of urinary calcium phosphate and xanthine crystals, respectively.

Novel approaches in the management of TLS include the use of urate oxidase. It is available for human use as an extract from *Aspergillus* (uricozyme) or a newer recombinant form named rasburicase (Elitek).[16,17] As shown in Figure 171-1, urate oxidase catabolizes uric acid into allantoin, which is approximately 10-fold more soluble than uric acid and thereby more easily excreted in the urine. Allopurinol is a xanthine oxidase inhibitor that blocks the conversion of hypoxanthine and xanthine to uric acid. Unfortunately, xanthine is even less soluble than uric acid, and preexisting uric acid is not affected by allopurinol. Rasburicase has a rapid onset of action and prevents uric acid–related complications, including acute renal failure. The primary but rare side effect of rasburicase is a hypersensitivity reaction. The principal advantage of rasburicase over allopurinol is its onset of action and lack of need for urine alkalinization, which can exacerbate the hyperphosphatemia so commonly seen in TLS.

171.8 SUGGESTED FURTHER READING*

A Altman: Acute tumor lysis syndrome. *Semin Oncol*. **28**(2 suppl 5), 2001, 3, *Moderately helpful review of human tumor lysis syndrome*.

O Bessmertny, LM Robitaille, MS Cairo: Rasburicase: a new approach for preventing and/or treating tumor lysis syndrome. *Curr Pharm Des*. **11**, 2005, 4177, *One of the best reviews of the use of rasburicase for the treatment and/or prevention of tumor lysis syndrome in humans*.

MB Davidson, S Thakkar, JK Hix, et al.: Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. *Am J Med*. **116**, 2004, 546, *Excellent and complete review of human tumor lysis syndrome*.

AA Yarpuzlu: A review of clinical and laboratory findings and treatment of tumor lysis syndrome. *Clin Chim Acta*. **333**, 2003, 13, *Excellent relatively up-to-date review of tumor lysis syndrome in humans*.

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* See the CD-ROM for a complete list of references

172 Chapter 172 Ocular Disease in the Intensive Care Unit

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172.1 KEY POINTS

- Ocular disease is a common manifestation of systemic illness seen in critically ill patients.
- Identification of ocular disease is completed by a thorough ophthalmic examination including indirect ophthalmoscopy, Schirmer tear testing, fluorescein staining, tonometry, and possibly cytologic studies, culture, or biopsy.

172.2 INTRODUCTION

Ophthalmic disease can be associated with or secondary to conditions that require a patient to be in a critical care facility. This chapter presents common ocular signs and discusses the appropriate interpretation of these signs and treatment of the ocular disease.

172.3 BLEPHAROSPASM

Blepharospasm is a nonspecific sign of ocular pain and may be associated with enophthalmos, elevation of the third eyelid, and spastic entropion. Both surface and intraocular disease can result in blepharospasm. The origin of ocular pain is determined by a thorough ophthalmic examination, including diagnostic tests such as fluorescein staining, Schirmer tear test evaluation, and tonometry. A topical anesthetic (e.g., 0.5% proparacaine) may facilitate examination by eliminating pain related to surface disease.

172.4 RED EYE

Veterinary clinicians will commonly encounter patients with a “red eye.” The redness represents new or congested blood vessels within the episclera, conjunctiva, or cornea. Episcleral vessels are stout, easily identifiable vessels that course perpendicular to the limbus and usually stop before reaching the limbus. Congestion of these vessels is associated most commonly with intraocular disease, specifically uveitis and glaucoma. However, with moderate to severe corneal disease these vessels may become engorged.

Conjunctival blood vessels are extremely fine; without the aid of magnification individual vessels are difficult to identify. When vessels are engorged, a pink-red flush is observable. Mild conjunctival hyperemia may be apparent with intraocular disease, but moderate signs are consistent with surface disease (i.e., conjunctivitis or keratoconjunctivitis). Differential diagnostic considerations for conjunctivitis include infections (canine distemper virus, feline herpes virus, feline *Chlamydophila,* leishmaniasis, onchocerciasis), allergies, postradiotherapy conditions, keratoconjunctivitis sicca (KCS), and exposure. Diagnosis is based on history and Schirmer tear test, fluorescein staining, cytologic studies, and biopsy results.

Conjunctival hyperemia can be easily confused with a conjunctival or subconjunctival infiltrate. This infiltrate may be fluid (chemosis) or cells. Mild chemosis is common with conjunctivitis. Severe chemosis may obstruct visualization of the cornea and intraocular structures. The most common cause of primary chemosis is topical toxicity (from neomycin, atropine, caustic agents). Removing the toxin and treating supportively will allow resolution of signs. Rarely, intravenous fluid overload at a rate of 2 to 3 times maintenance for a period of 2 days or longer can result in marked chemosis. Tapering the fluid rate will allow the chemosis to resolve.

Subconjunctival infiltrates may cause the conjunctiva to appear thickened. They may be focal or diffuse. Carefully examining the color of the conjunctiva may help differentiate an infiltrate from common hyperemia.

A diffuse yellow appearance of the conjunctiva in the absence of thickening is consistent with icterus. This may be the first clinical sign of icterus and should prompt the clinician to pursue further diagnostic tests concerning hepatobiliary status.

Neoplastic cells within the subconjunctiva frequently result in thickening and a yellow to orange hue. Lymphoma is the most common neoplasia presenting in the subconjunctiva and may represent the primary tumor site. Other masses observed in the subconjunctiva include systemic histiocytosis (orange), hemangiosarcoma (red), melanoma (brown), and granulomatous scleritis (pink). A definitive diagnosis can usually be obtained by biopsy. Light sedation and topical anesthesia are typically all that is needed to obtain a diagnostic sample.

Subconjunctival hemorrhage in a critically ill patient, observed as petechiae or ecchymoses, warrants investigation for an underlying coagulopathy. Hemorrhage may be isolated to the subconjunctiva or seen in the anterior chamber (hyphema). Causes of hemorrhage not associated with a coagulopathy include trauma, strangulation (choke collars), and rarely constipation.

A blue-green discoloration of the sclera and/or conjunctiva may be observed. This has been observed in dogs receiving mitoxantrone chemotherapy. Signs are temporary and usually resolve within hours to days after cessation of treatment.

172.5 TEAR FILM ABNORMALITIES

The tear film is comprised of three layers: an outer lipid layer, middle aqueous layer, and an inner mucin layer. A deficiency in any of these components may result in decreased tear production or increased tear clearance (evaporation) and may be diagnosed with a Schirmer tear test.

Clinical signs of a tear film abnormality depend on the severity, chronicity, and underlying cause of the tear deficiency. The most consistent and obvious finding is a thick mucoid discharge, commonly accumulated on and around the eyelids. Additional clinical signs include conjunctival hyperemia, a lackluster appearance to the corneal surface, and in chronic cases corneal vascularization and melanosis. Chronic tear film deficiencies lead to thickening of the corneal epithelium, and therefore ulceration is not common. However, the critically ill patient may develop acute KCS resulting in rapid, severe, and potentially globe-threatening corneal ulcers.

There are numerous causes of decreased tear production (KCS) and increased tear clearance. Undoubtedly the most common cause of KCS is immune-mediated destruction of the lacrimal gland and gland of the third eyelid. This will likely be a preexisting disease in critically ill patients. Treatment with topical cyclosporine and artificial tear ointments should be continued.

Other causes of decreased tear production include radiation therapy, drug toxicity (sulfonamides, atropine, etodolac), chronic blepharoconjunctivitis, general anesthesia, orbital trauma, neurogenic, and congenital (Yorkshire Terrier, Pug) and, rarely, secondary to an endocrine disorder (hypothyroidism, diabetes mellitus, hyperadrenocorticism).

Megavoltage radiation near the orbit resulted in KCS in 24% of dogs within 1 to 6 months of therapy secondary to direct destruction of glandular tissue.[1] Medical therapy is solely supportive, including the application of artificial tear ointments (petroleum, lanolin, mineral oil base) and gels as frequently as possible.

Sulfa-containing drugs are well known to decrease aqueous tear production, with 65% of patients having decreased tear production, 15% with clinical signs of KCS.[2] Sulfonamides should be used with caution in small breeds, brachycephalic breeds, and those breeds predisposed to KCS. Stopping therapy at the onset of KCS may allow lacrimal function to return in some patients. An idiosyncratic reaction resulting in irreversible, absolute xerophthalmia has been demonstrated in a small percentage (0.0003%) of dogs receiving etodolac. Patients should have a normal Schirmer tear test result before treatment and should be monitored closely during therapy. Any decrease in tear test results warrants cessation of oral therapy and initiation of topical therapy.

General anesthesia, especially with atropine as a premedication, dramatically decreases aqueous tear production that may persist for 24 hours.[3] Many patients receive a topical lubricant before anesthesia but rarely afterward. A topical lubricating ointment should be applied at least every 4 hours for 24 hours following anesthesia to decrease ocular surface drying that may lead to corneal ulceration.

Neurogenic KCS results from disruption of the parasympathetic fibers coursing with the facial and trigeminal nerves to the lacrimal gland. Clinical signs are similar to those of immune-mediated KCS, except that in these cases dysfunction is usually unilateral. If the lesion is near the pterygopalatine ganglion, the caudal nasal nerve will also be affected and a dry, crusty nose ipsilateral to the dry eye will be noted. Treatment is aimed at stimulating the denervated gland to secrete aqueous tears. Oral 4% pilocarpine (1 drop/4.4 kg PO q12h and increased slowly to effect) may be effective, although there is a fine line between a therapeutic and a toxic dose. Signs of toxicity include vomiting, diarrhea, and ptyalism. Treatment with topical lubricants and cyclosporine is also warranted.

Increased tear clearance secondary to evaporation accounts for most cases of dry eye in the intensive care patient. Increased evaporation may be secondary to a tear lipid deficiency, lagophthalmos, or decreased reflex tearing. Meibomianitis, blepharitis, and conjunctivitis damage the meibomian glands or conjunctival goblet cells, resulting in instability of the tear film. Treatment with mucinomimetic preparations such as 1% to 2% methylcellulose or sodium hyaluronate will help restore tear film stability.

Lagophthalmos is the inability to completely close the eyelids and may be a conformational (brachycephalic breeds, cicatricial ectropion, eyelid agenesis) or neurologic (facial or trigeminal nerve dysfunction, obtundation) disorder. The lack of a consistently complete palpebral reflex is diagnostic. With lagophthalmos, the tear film is exposed and rapidly evaporates, especially in the interpalpebral fissure. Obtunded animals frequently have decreased or absent palpebral reflexes and decreased reflex tearing, which further complicates the tear deficiency. Regardless of the cause, hourly application of an artificial tear ointment or gel is necessary. Left untreated, progressive corneal ulceration will ensue. Chronic cases (e.g., ventilator patients) may require a lateral temporary tarsorrhaphy.[4]

172.6

ABSENT PALPEBRAL REFLEX

Absence of the palpebral reflex is due to either loss of trigeminal nerve function (the afferent arm) or facial nerve paralysis (the efferent arm). In addition to loss of palpebral reflex, signs associated with facial nerve paralysis in cats and dogs include lowered carriage of the ear, drooping of the eyelids with resultant widening of the palpebral fissure, and increase in scleral visibility on the affected side, as well as “pulling” of the nose toward the normal side.

Because the lacrimal nerve runs with the facial nerve over a portion of its course, Schirmer tear test values should be monitored in patients with facial nerve paralysis. Severe corneal disease may be associated with facial nerve paralysis. Causes of facial nerve paralysis include trauma, neoplasia, and head or neck surgery. Depending on the cause, the signs of facial nerve paralysis may resolve spontaneously. Because the retractor bulbi muscle is innervated by the abducens nerve, many patients learn to “blink” with their third eyelid by retracting their globes. Treatment for facial nerve paralysis is frequent (q4-6h) application of lubricating ointments.

The trigeminal nerve provides sensory innervation to the ocular surface and eyelids. Disruption of this innervation may result in severe keratitis. The most common cause of trigeminal nerve loss is orbital trauma.[5] Unlike those with facial nerve paralysis, these patients do not “blink” with their third eyelids because they do not have any sensation of ocular surface dryness. Treatment for ocular problems related to trigeminal nerve compromise is supportive care of the cornea with topical lubricants.

172.7 CORNEAL CHANGES

Corneal clarity is sacrificed when there is disruption of the normal organization of stromal collagen lamellae, in-growth of blood vessels, or deposition of pigment or cells. Epithelial cell loss usually results in focal corneal edema, although expansive defects can result in diffuse edema. Corneal endothelial cell dysfunction causes diffuse edema and is secondary to intraocular disease, specifically uveitis or glaucoma. A thorough ophthalmic examination including fluorescein staining and tonometry will aid in differentiating the underlying cause.

The normal cornea is avascular and receives nutrition from the tear film and aqueous humor. Therefore the presence of blood vessels indicates ongoing pathology. Superficial corneal blood vessels appear as fine tree branches and are consistent with superficial disease (superficial corneal ulceration, KCS, exposure keratitis, pannus). Deep corneal blood vessels have the appearance of hedges, with individual vessels difficult to identify. These vessels are present with deep corneal (stromal) or intraocular (uveitis, glaucoma) disease. With disease, vessel in-growth is delayed for approximately 2 to 4 days, and then vessels advance approximately 1 mm per day. Therefore length of the vessels can aid in determining the chronicity of disease.

Corneal ulceration is likely the most commonly encountered primary ophthalmic disease in the intensive care patient. Clinical signs include blepharospasm, conjunctival hyperemia, episcleral congestion, mucoid to mucopurulent discharge, focal to diffuse corneal edema, an observable corneal defect, and potentially vascularization, abscess formation, or malacia. Diagnosis is facilitated with application of fluorescein stain. Stromal loss, cellular infiltrate, moderate vascularization, and progression despite medical therapy indicate complications (Color Plate 172-1).

The leading cause of complicated ulcers is the use of topical steroids in a patient with a corneal defect. Complicated ulcers require strict monitoring and aggressive medical and potentially surgical therapy. Therefore referral to or consultation with an ophthalmologist is recommended.

When approaching a complicated ulcer, determination of the depth of the defect is the first step. This can be accomplished using the slit beam on the direct ophthalmoscope and looking at the change in curvature of the light beam. Other hints include location of corneal blood vessels (see previous discussion) and fluorescein staining characteristics. If stain is observed only along the walls, but not the floor, a descemetocele is present and immediate referral to an ophthalmologist is recommended.

After determination of the depth, samples should be obtained for aerobic bacterial culture and cytology.[6] Initial therapy should include a broad-spectrum topical antibiotic (dependent on culture and cytology results) at least every 4 hours, topical atropine every 12 hours, and an Elizabethan collar. If cellular infiltrate or malacia are present, a more powerful topical antibiotic such as ciprofloxacin should be initiated every 2 hours along with topical serum every 2 hours. Serum can be harvested from the patient or a healthy donor of the same species. Serum must be kept refrigerated and a new batch should be harvested once weekly to prevent contamination.

Fortunately, most corneal ulcers are not complicated. A topical triple antibiotic preparation applied 2 to 4 times daily, a single dose of atropine, and an Elizabethan collar are usually sufficient. Epithelialization of uncomplicated ulcers occurs within 3 to 5 days. If healing has not occurred within this time, either the ulcer has become complicated or the underlying cause (ectopic cilia, distichiasis, conjunctival or third eyelid foreign body) has not been identified.

Corneal infiltrates other than white blood cells associated with infected ulcers are rare. Notable exceptions include neoplastic cells, mineral, and lipid. Circumferential, severe perilimbal vascularization with a yellow-orange corneal infiltrate along the leading edge of the vessels may represent lymphoma. Cholesterol crystals and lipid may be deposited in an arclike fashion (arcus lipoides) in the anterior corneal stroma. Often this represents a systemic dyslipidemia, and further diagnostic tests to investigate the cause are warranted. Otherconcurrent signs may include lipemic aqueous or lipemia retinalis. Differential diagnostic considerations include hypothyroidism, diabetes mellitus, hyperadrenocorticism, pancreatitis, and a primary hyperlipidemia.

172.8

ANTERIOR CHAMBER ABNORMALITIES

Changes in the appearance of the anterior chamber most often are due to alterations in the composition of the aqueous. The aqueous is essentially modified blood with protein and cells removed in the ciliary body. Under conditions of anterior uveitis, these elements gain entry into the aqueous humor, producing the signs of aqueous flare (protein), keratic precipitates (fibrin and white blood cell aggregates on the posterior cornea), hyphema (red blood cells), and hypopyon (white blood cells) (Color Plates 172-1 and 172-2).

Although all of these conditions are nonspecific indicators of anterior uveitis, keratic precipitates, hyphema, and hypopyon are seen frequently with certain causes of anterior uveitis. Keratic precipitates are often a sign of feline infectious peritonitis (FIP), lymphoma, or systemic fungal infections. Hyphema frequently is associated with systemic hypertension, coagulopathies, and corneal perforations. Hypopyon is often seen with causes of anterior uveitis that lead to an outpouring of white blood cells, such as systemic fungal or bacterial infections and lymphoma.

Treatment for anterior uveitis should be aimed at both the underlying systemic ailment and the ophthalmic disease. Antiinflammatory agents are indicated. Prednisolone acetate (1% suspension) or dexamethasone (0.1% either suspension or ointment) administered every 2 to 12 hours depending on severity are excellent choices for topical therapy. Hydrocortisone is relatively impotent and poorly absorbed when applied topically and is not a suitable antiinflammatory agent for treatment of anterior uveitis.

Topical nonsteroidal ophthalmic medications are also available, namely flurbiprofen (0.03% solution) and diclofenac (0.1% solution). These are good alternatives to topical steroid preparations if corneal ulceration is present or systemic conditions prevent the use of steroids. Systemically administered steroidal and nonsteroidal drugs reach the anterior uvea and can be helpful adjuncts, especially in severe cases. Topical atropine (1% solution or ointment) may be indicated in the treatment of anterior uveitis by relieving the pain associated with iris sphincter 741 and ciliary body muscle spasms and by preventing posterior synechia. However, it must be used with caution and intraocular pressure must be closely monitored during its use because it can exacerbate glaucoma, especially in dogs.

172.9 PUPIL ABNORMALITIES

Pupil abnormalities may or may not be associated with other ophthalmic disease. They are divided into four clinical presentations: anisocoria, miosis, mydriasis, and dyscoria.

172.9.1 Anisocoria

Anisocoria is defined as unequal pupil size. Although usually easy to detect, it can be challenging to ascertain which pupil is abnormal. Careful observation of pupil size in ambient light and dim illumination and pupil reaction under stimulation with a bright light source will usually allow for this determination. Once it has been determined which is the affected pupil, the next step is to investigate the causes of miosis or mydriasis.

172.9.2 Miosis

Pupil size in mammals is the product of the balance between parasympathetic tone on the iris sphincter muscle and sympathetic tone on the iris dilator muscle. Therefore miosis is the result of stimulation of the iris sphincter, loss of sympathetic tone of the iris dilator, or both. Although miosis may be produced with topical medications, namely, pilocarpine and latanoprost, there are two conditions that cause miosis: anterior uveitis and Horner's syndrome. Fortunately, these two causes are easily distinguished from one another on the basis of associated ophthalmic signs.

In addition to miosis, signs often associated with anterior uveitis include blepharospasm, epiphora, episcleral injection, 360-degree corneal vascularization, corneal edema, aqueous flare, keratic precipitates, hypopyon, and hyphema. Anterior uveitis is the most common ophthalmic manifestation of systemic disease and is often present in critically ill patients. Common diseases that can cause anterior uveitis in cats and dogs are systemic infectious disease (fungal, bacterial, viral, rickettsial, and algal), primary or secondary neoplasia, blunt or penetrating trauma, and immune-mediated conditions. Treatment for anterior uveitis is covered earlier in this chapter under Anterior Chamber Abnormalities.

The signs associated with Horner's syndrome are secondary to compromise of the sympathetic innervation to the eye and consist of a triad of signs in cats and dogs: ptosis, miosis, and third eyelid protrusion secondary to enophthalmos (Color Plate 172-3). Although ptosis and third eyelid protrusion can mimic blepharospasm, the eyes of patients with Horner's syndrome are comfortable and noninflamed. Horner's syndrome is frequently idiopathic, but it can occur secondary to otitis interna or media, trauma or surgery to the side of the face or neck, and intracranial or thoracic neoplasia.[7,8] Pharmacologic testing can localize the lesion in Horner's syndrome and is described in detail elsewhere.[9,10] Treatment of Horner's syndrome is accomplished by identifying and addressing the underlying cause, if possible. No specific ophthalmic therapy is indicated.

172.9.3 Mydriasis

Mydriasis is due to stimulation of the iris dilator muscle or compromise of the parasympathetic tone of the iris sphincter muscle, or both. As with miosis, mydriasis can be pharmacologically induced with agents such as atropine. However, unlike miosis, mydriasis is associated with many conditions. Highly stressed patients, particularly cats, can have dilated pupils and poor to absent pupillary light responses (PLRs). Likewise, aged patients with iris atrophy may have mydriasis in one or both eyes. Optic nerve or end-stage retinal disease can lead to mydriasis. For causes of these conditions see the Blindness section below.

Mydriasis is a consistent sign of glaucoma, and intraocular pressure should be measured in all patients with dilated pupils. The most common cause of glaucoma in critically ill patients is anterior uveitis. Glaucoma is painful and blinding, and steps should be taken immediately to lower intraocular pressure. If the patient's systemic condition allows it, mannitol (20% to 25% solution) administered intravenously at a dosage of 1 to 2 g/kg can produce a dramatic drop in intraocular pressure. Other effective glaucoma medications include methazolamide (5 mg/kg PO q12-24h), dorzolamide solution (q8-12h topically), and latanoprost solution (q12-q24h topically).

Mydriasis is also a consistent finding in dysautonomia (Key-Gaskell syndrome), which is most frequently seen in cats,[11] although a similar syndrome has been reported in dogs.[12] In addition to mydriasis, signs associated with this condition include anorexia, depression, weight loss, dehydration, bradycardia, constipation, protrusion of both third eyelids, and decreased tear production. Pharmacologic testing to verify the diagnosis is described elsewhere.[13] Treatment for the ocular component of dysautonomia consists of topical lubrication.

The unique parasympathetic innervation of the feline pupil can produce a variation in mydriasis, the D-shaped or reverse D-shaped pupil in which only one half of the pupil dilates. This defect is due to lesions involving the medial or lateral short ciliary nerve and is commonly associated with feline leukemia virus.

172.9.4 Dyscoria

Dyscoria is defined as an irregularly shaped pupil. This is most commonly secondary to posterior synechiae, a result of anterior uveitis.

172.10 BLINDNESS

Visual capability commonly is assessed by eliciting a menace response, observing the patient tracking a cotton ball dropped repeatedly within its visual range or performing a maze test. Unfortunately, verification of visual status is often problematic for the critical care practitioner because many seeing patients appear to fail these routine tests because of either alterations in mentation or inability to ambulate.

Blindness can occur as a result of disease in one of five anatomic locations: (1) cornea, (2) lens, (3) retina, (4) optic nerve or tracts, and (5) brain. Blindness due to corneal changes is readily apparent and causes of alterations in corneal transparency are covered elsewhere in this chapter. Causes of cataracts associated with serious systemic disease include diabetes mellitus and anterior uveitis. However, neither of these would likely lead to cataract formation over the period that a patient would be hospitalized in a critical care setting.

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A number of systemic conditions can lead to retinal disease and vision compromise. PLRs are often present, even in advanced retinal disease. Therefore normal PLRs do not rule out retinal disease as a cause of vision impairment. Retinal conditions associated with vision compromise secondary to systemic disease are manifested most frequently as retinal separation, retinal hemorrhage, or retinal inflammatory cellular infiltrates. Retinal separations frequently are classified by the nature of the subretinal fluid: serous, hemorrhagic, or exudative (Color Plate 172-4). The type of fluid under the separation can provide clues as to the underlying cause.

Systemic conditions that may manifest with a serous retinal separation include systemic hypertension (early) and autoimmune disease, such as uveodermatologic syndrome in dogs. Typical causes of hemorrhagic retinal separation and intraretinal hemorrhage include systemic hypertension, rickettsial disease (Rocky Mountain spotted fever, *Ehrlichia* infection), toxic coagulopathies with rodenticides, vasculitis (FIP), immune-mediated hemolytic anemia, and hyperviscosity syndrome. Exudative retinal separation and intraretinal inflammatory cellular infiltrates are commonly an expression of systemic fungal disease, neoplasia (especially lymphoma), toxoplasmosis, viral diseases (canine distemper, feline leukemia virus, feline immunodeficiency virus, FIP), and protothecosis.

In cats, acute blindness has been associated with systemic enrofloxacin at dosages as low as 4 mg/kg PO q12h.[14] This is manifested by diffuse tapetal hyperreflectivity and retinal vascular attenuation without signs of retinal separation or retinal cellular infiltration. The extent of vision impairment with all of these conditions depends on the extent of retinal involvement. For virtually all of these conditions, there is no specific treatment of the ocular component beyond addressing the underlying systemic cause.

Optic nerve disease can lead to blindness and may be associated with a number of systemic illnesses. Unlike retinal causes of vision impairment, blindness due to optic nerve disease usually is accompanied by loss of PLRs and mydriasis. Optic nerve disease may or may not be manifested by changes in the appearance of the optic disc. When present, ophthalmoscopic signs of optic nerve disease include optic disc swelling, fuzzy and indistinct disc borders, and hemorrhages on the disc or in the peripapillary area (Color Plate 172-5).

Systemic diseases with the potential for optic nerve involvement include granulomatous meningoencephalitis, canine distemper, lymphoma, systemic fungal infection (especially cryptococcosis), meningioma, ivermectin overdose,[15,16] and hyperviscosity syndrome. Treatment is aimed at the underlying systemic cause.

Blindness secondary to involvement of the visual center in the occipital cortex is rare in cats and dogs. Affected animals usually have marked neurologic deficits.

172.11

SUGGESTED FURTHER READING*

KN Gelatt, A van der Woerdt, KL Ketring, et al.: Enrofloxacin-associated retinal degeneration in cats. *Vet Ophthalmol*. **4**, 2001, 99, *A case series of 17 cats that received systemic enrofloxacin and shortly after developed retinal degeneration; excellent fundic photographs*.

IP Herring, JP Pickett, ES Champagne, et al.: Evaluation of aqueous tear production in dogs following general anesthesia. *J Am Anim Hosp Assoc*. **36**, 2000, 427, *An article that describes the effects of anesthesia on tear production, the duration of those effects, and factors contributing to the severity of the effects*.

KD Hopkins, KL Marcella, AE Strecker: Ivermectin toxicosis in a dog. *J Am Vet Med Assoc*. **197**, 1990, 93, *A case report of the clinical signs (both systemic and ophthalmic), diagnosis, and treatment of a dog with ivermectin toxicosis*.

TJ Kern, MC Aromando, HN Erb: Horner's syndrome in dogs and cats: 100 cases (1975-1985). *J Am Vet Med Assoc*. **195**, 1989, 369, *A retrospective study of the signs, causes, diagnosis (including pharmacologic testing), and treatment of Horner's syndrome in dogs and cats*.

* See the CD-ROM for a complete list of references.

173 Chapter 173 Air Embolism

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173.1 KEY POINTS

- Air embolism occurs when a pocket of gas enters or is formed within the vascular compartment and subsequently forms an obstruction to blood flow.
- Intravenous catheter placement and use, laparoscopy, some surgeries, and hyperbaric therapies can all be associated with this complication.
- Prevention of air embolism is a priority because detection is difficult and tends to be delayed until after the embolism is dangerously large.
- Capnography and esophageal Doppler probes are the most useful tools for early detection of air embolism.
- Oxygen administration is recommended in patients with air embolism. Manual reduction involves aspirating the air from the embolus or reducing the size of air bubbles to allow perfusion around the bubbles.

173.2 INTRODUCTION

Because most veterinary patients do not scuba dive, air embolism is almost entirely an iatrogenic phenomenon in veterinary medicine. Because the simplest procedures, such as intravenous injection, have the potential to cause this calamity, it is important to consider the ramifications. The pathophysiology is determined by the size of bubbles and rate of intravenous gas entry.

Massive air embolism in the heart creates an absolute obstruction to blood flow; the compressible envelope of air contracts and expands with the working of the heart, and no blood gains entry to the air-filled chamber. Smaller air emboli wedge into vessels, creating focal areas of ischemia or leading to ventilation-perfusion mismatching if located in the lungs. With a continuous influx of air, small emboli coalesce into larger air pockets. Air emboli in the cerebral vasculature subject this vulnerable organ to hypoxemia, which, along with coronary artery emboli, marks the most severe consequence of small bubble gas embolization.

When an embolus is discrete enough to allow circulation to persist, gas is absorbed into the tissues, eventually reducing the volume of the embolism until it is completely dissolved or small enough to move to a more distal tissue bed. For this reason, the type of gas present in the bubble can have a tremendous impact on the amount of ischemia, as does the tissue bed in which the bubble becomes lodged. Administration of extremely insoluble gases (such as nitrous oxide) exacerbates gas emboli because the insoluble gas escapes from the blood and diffuses into the air pockets, causing expansion.[1]

Redundant blood flow salvages the lungs from significant damage from many small air emboli, and the lungs serve as the primary sponge for venous air emboli. A constant influx of air can overload this “filter” for emboli, allowing bubbles to emerge into the arterial system. In dogs, this occurs in 50% of animals when 0.35 ml/kg/min of air is infused.[2] Furthermore, lodging of air emboli in the lungs is not necessarily benign and may cause focal injury, edema, and the subsequent release of vasoactive mediators. Eventually this can culminate in alveolar collapse, atelectasis, and impaired gas exchange.[3]

173.3 GAS EMBOLISM RESULTING FROM INTRAVENOUS ACCESS MISHAPS

In ordinary-sized patients, it is somewhat difficult to introduce enough air to create a clinically apparent embolism. Pigs have tolerated 2 ml/kg of air without irreversible hemodynamic collapse.[1] However, pigs have a reduced ability to remove air during infusions when compared with dogs. Air delivery rate of only 0.1 ml/kg/min was associated with bubbles breaking through to the arterial system in pigs, whereas dogs tolerated up to 0.35 ml/kg/min.[1,4] Extrapolating from the pig single-dose data, a 1-kg dog can probably tolerate up to approximately 2 ml of air as a single dose before cardiovascular collapse occurs.

The risk of air embolism is increased when venous access sites are located higher than heart level. This can occur in standing dogs and cats during jugular catheterization or puncture, or when ear catheters are used. Great care should be taken in placing jugular catheters in very small patients, in which a small amount of air could rapidly prove fatal.

In larger dogs and cats, embolization generally occurs when elevated catheters are left open to room air or become disconnected from a sealed system. Air moves into the relatively negative intravascular space, causing air entrainment with subsequent coalescence into a complete venous or cardiac obstruction. Because this usually occurs with patients in room air, the bulk of the embolus is composed of nitrogen gas. Nitrogen is relatively poorly soluble in tissues, so it takes several minutes for a nitrogen embolus to dissipate.[5]

Small air bubbles are often administered during intravenous injections and fluid therapy, but these are well tolerated in ordinary individuals. However, larger volumes of air may be mistakenly administered via intravenous tubing or extension sets that were not appropriately flushed, and in small patients this can be sufficient to cause irreversible damage.

Air emboli have also been known to form when intravenous fluid bags are placed under pressure. Most fluid bags contain a small amount of air that can be delivered when the entire contents of the bag are pressurized for rapid delivery to a patient. Increased caution is warranted in patients with a right-to-left cardiac shunt because the lungs may not filter out air bubbles; consequently these individuals may suffer from focal cerebral infarctions when even the smallest air bubbles are administered or allowed to form. 744 745

173.4 GAS EMBOLIZATION RESULTING FROM LAPAROSCOPIC PROCEDURES

Laparoscopy has gained enormous popularity as a less invasive method to diagnose or treat many conditions. However, this procedure requires the introduction of a sizeable volume of gas into the body cavity of interest. When this gas exists at a pressure midway between venous collapse and the intravenous pressure, it is then free to move into the vascular bed servicing the inflated region. To minimize the impact of gas bubble formation during laparoscopy, carbon dioxide is generally chosen as the inflation gas. Carbon dioxide can still form emboli, but because it is absorbed rapidly into tissues, it seldom causes clinical problems (0.001% to 0.59% incidence in humans).[6]

In theory, in order for an embolus to enter the venous system during laparoscopy there would have to be a defect in a vein or other vascular bed. If the intraabdominal inflation pressure matched the intravenous pressure, air could gain access to the circulation. If the inflation pressure was high enough to collapse the vein, air entrainment would cease, and if the inflation pressure was lower than venous pressure there would be hemorrhage from the vein without air entrainment. In general, inflation pressures higher than 15 mm Hg are not recommended during laparoscopy.[6] Under normal conditions, veins collapse at 20 to 30 mm Hg; this is significantly higher than the recommended intracompartmental pressure. Therefore when using recommended inflation pressures, transected vessels should hemorrhage rather than entrain gas. Another factor that allows early detection of air embolism is slowing abdominal insufflation to rates less than 1 L/min.[7]

Even with these precautions, embolization during laparoscopy occasionally occurs. As previously mentioned, carbon dioxide is therefore generally used as the inflation gas. Rapid and complete ligation or cauterization of any venous injury will also limit the access points for gas emboli. Emboli are certainly a risk of laparoscopy, and monitoring for them is important during all laparoscopic procedures.

173.5 GAS EMBOLIZATION DURING SURGERY

As occurs with catheterization, gas embolization during surgery is most likely when the surgical site is higher, gravitationally speaking, than the heart. This situation may occur with most forms of neurosurgery (craniotomy and spinal surgeries) and many orthopedic surgeries (fracture repairs). Air entry is permitted via open veins or sometimes through bony routes (sinuses and long bones). Nitrogen is the predominant gas in room air, so slow absorption of entrained air can be anticipated.

Prevention begins with surgical positioning to avoid excessive elevation of the surgical site. When this is not possible, keeping the surgical site filled with isotonic fluids will prevent gas from entering the bloodstream. In human neurosurgery, patients are often placed in a sitting position. Elevation of central venous pressures using positive end-expiratory pressure and volume loading reduces the incidence of air embolism in human and animal models.[6,8] Craniotomy positioning in dogs and cats likewise results in surgical site elevation over the level of the heart.

Cardiopulmonary bypass is notorious for the introduction of air into the circulation. This air entry is extremely difficult to control, because it arises from both the equipment functioning as the circulatory circuit and the surgery itself.[9] In humans, a large proportion of postbypass complications are attributed, in part, to emboli or microemboli. Although unreported, the incidence may be even higher in veterinary patients, because their smaller size magnifies the effect of the minutest air bubbles. Furthermore, many of these emboli are arterial, so consequences can include cerebral and coronary artery obstruction.

173.6 GAS EMBOLIZATION DURING HYPERBARIC THERAPY

As mentioned before, domestic dogs and cats seldom scuba dive or are subjected to dramatic increases in barometric pressure. One exception may be during intentional hyperbaric treatment for conditions such as anaerobic infections and inflammatory conditions. In a hyperbaric setting, gases dissolve more readily into tissues. When the pressure returns to normal these gases rapidly leave the tissues and form bubbles. When hyperbaric therapy is used, careful attention to recommended protocols is key. Even when protocols are followed, some individuals may experience embolism from gases emerging from a dissolved state into the bloodstream or other organs. Appropriate evaluation, detection, and decompression therapy by qualified individuals are important to reduce the impact of this sequela. Unfortunately, there is unpredictable individual variation as to when this occurs.

173.7 DETECTION OF AIR EMBOLI

Air emboli should be considered a risk in any situation in which air can be introduced by equipment or error, or when a surgical procedure produces an incised vascular bed with a hydrostatic pressure gradient favoring venous entry. Neurologic signs of air embolism are difficult to detect in animals, with the exception of seizures, unconsciousness, or a poor, prolonged recovery. An astute observer might detect restlessness, agitation, or change in demeanor in a conscious patient. Distinctive Doppler sounds may be heard over the heart or large vessels after 0.5 to 2 ml/kg air has entered the venous system, and the sound is described as a *mill-wheel murmur*. Tachypnea results from air emboli due to vagally mediated and nonvagally mediated mechanisms, and an anesthetized patient that is not paralyzed may become tachypneic or begin to breathe over the ventilator even before the onset of hypoxemia.[5] Unfortunately, air embolism in animals is often detected by the subsequent cardiovascular collapse. Clearly this is a late sign.

Transesophageal echocardiography can be a helpful tool for diagnosing intracardiac air embolism before cardiac arrest. Furthermore, with close intraoperative monitoring a classic progression of signs may be observed. In every breath an individual takes, a quantity of that breath exits from regions where gas is not exchanged. This is known as *dead-space ventilation*. Many factors can alter dead space-to-alveolar ventilation, but the ratio is generally thought to be around 30%.[10] When a region of blood flow through the lungs is abolished, a new region of dead space is created, and there will be an acute fall in the end-tidal carbon dioxide ($ETCO_2$) level, and an increase in measured arterial carbon dioxide ($PaCO_2$).[11]

$$\%\ \text{Dead space} \approx (PaCO_2 - ETCO_2) \div PaCO_2$$

Simultaneously, blood flow will be routed through regions of the lung that are less ventilated, increasing physiologic shunt and decreasing oxygenation. An acute increase in pulmonary pressures and decrease in lung compliance will occur following air embolization in the lungs.[11] This is recognized as the delivery of lower tidal volumes at inspiratory pressures that previously accomplished normal ventilation. This does not occur if the embolism is composed of carbon dioxide. Computed tomography and magnetic resonance imaging may be helpful to detect emboli, but are neither guaranteed nor time efficient in a crisis.[12] Therefore clinical assessment is generally preferred.

173.8 TREATMENT OF AIR EMBOLISM

Immediate attention toward interrupting further air entrainment is the most important goal of treatment. Once further intravascular gas flow is prevented, a venous air embolism may resolve, and the pulmonary “filter” may be sufficient to prevent further arterial spillover of air. If nitrous oxide is being administered, it should be discontinued immediately.[1] When possible, manual reduction of an air embolism can rapidly restore circulation. The goal is to place a catheter in the embolus and aspirate air or foam, a process that is conveniently diagnostic as well as therapeutic.

Oxygen administration will treat hypoxemia and also provide a diffusion gradient if the embolized gas is anything other than oxygen.[1,13] Work in pigs does not support hyperventilation, but ventilatory support is still recommended because of the increased work of breathing associated with pulmonary air embolism.[3] Immediately after embolization, blood pressure may become transiently high, which will facilitate movement of air bubbles into venous locations. Progressive hypotension is lethal, causing increased bubble entrapment and reductions in coronary and cerebral blood flow and thus compromising the organs most susceptible to anoxia.[13] The goal is to establish and maintain normotension.

Much controversy exists as to the usefulness of hyperbaric oxygen therapy for reversing gas emboli. Animal studies have given mixed results.[3] Overall, if hyperbaric oxygen therapy is available, early intervention is necessary for a beneficial effect.

The use of drugs in the treatment of patients with gas embolism is controversial. Hemodilution with colloid fluids improves neurologic recovery, with a target packed cell volume of 30%.[14] Crystalloid fluids are not recommended because of their propensity to exacerbate cerebral edema. If seizures occur, barbiturates are recommended in lieu of benzodiazepines because of improved inhibition of catecholamines and reduction in oxygen consumption and intracranial pressure.[3] Heparin has a theoretic advantage in preventing platelet clumping after endothelial damage, but mixed results have been reported in the literature.[3] Glucocorticoids are not recommended because they appear to increase vessel occlusion and infarct size. Intravenous lidocaine has been shown to improve cerebral function and decrease infarct size in several studies.[3]

On the cutting edge, fluorocarbons are solutions with high gas-dissolving capability. When administered intravenously these compounds could improve oxygenation and simultaneously help shrink gas emboli.[2] Finally, work is being done to evaluate compounds that alter surface tension because aspherical emboli tend to have higher internal bubble pressure, thereby speeding their reabsorption time.[9]

Essentially, preventing gas emboli is key. Failing this, early diagnosis using paired $ETCO_2$ and $PaCO_2$ measurements or Doppler echocardiography improves survival. Treatment targets reduction of bubble size by a variety of mechanisms followed by cerebral protective maneuvers.

173.9 SUGGESTED FURTHER READING*

J Joris: Anesthesia for laparoscopic surgery. In RD Miller (Ed.): *Miller's anesthesia*. ed 6, 2005, Churchill Livingstone, Philadelphia, *The anesthesia "bible," this book provides in-depth discussion of a milieu of anesthesia-related information*.

AB Lumb: In *Nunn's applied respiratory physiology*. ed 6, 2005, Butterworth-Heinemann, Oxford, *The "bible" of respiratory physiology*.

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* See the CD-ROM for a complete list of references.

174 Chapter 174 Critically Ill Pediatric Patients

Maureen McMichael, DVM, DACVECC

174.1 KEY POINTS

- There are significant differences in the biochemical, hematologic, radiographic, pharmacologic, and monitoring parameters in neonatal and pediatric animals.
- Dramatic elevations in alkaline phosphatase and γ-glutamyl- transferase and very low values for serum blood urea nitrogen, albumin, and cholesterol occur in the neonate and can mimic hepatic failure.
- The most common causes of dehydration in the neonate and pediatric patient are gastrointestinal losses and insufficient intake.

174.2 INTRODUCTION

There are several crucial differences in the diagnosis, monitoring, and treatment of critically ill neonates and pediatric patients compared with critically ill adult patients, and it is essential for veterinarians with a neonatal and pediatric patient base to become familiar with normal biochemical, hematologic, radiographic, and physical examination values for this age range. In veterinary medicine, the term *neonate* encompasses birth to 2 weeks of age, and the term *pediatric* refers to animals between 2 weeks and 6 months of age. This chapter will review the hematologic, biochemical, nutritional, imaging, fluid treatment, monitoring, and pharmacologic aspects of the normal and critically ill neonate and pediatric cat and dog. Also included is a brief review of sepsis in the neonate.

174.3 PHYSICAL EXAMINATION FINDINGS

Healthy neonates are lively and plump (Box 174-1). Illness often is recognized by incessant crying, lethargy, limpness, and poor muscle tone. Mucous membranes are often hyperemic during the first 4 to 7 days of life and may be pale, cyanotic, or gray in sick neonatal animals. The rectal temperature at birth is normally 95.4° to 98.6° F and gradually increases to adult levels over 4 weeks.

By pediatric stethoscope (ideally), many puppies and kittens will be found to have an innocent murmur until 12 weeks of age. However, other causes of a murmur include a congenital cardiac defect, stress, fever, sepsis, anemia, or hypoproteinemia. The heart rate in the normal neonatal puppy and kitten is 200 and 250 beats/min, respectively. The heart rate decreases as the animal develops increased parasympathetic tone at 4 weeks of age. The respiratory rate following birth is normally 15 breaths/min but increases to 30 breaths/min within 1 to 3 hours. Because of the small tidal volume and increased interstitial fluid in the normal neonate, assessment of lung sounds is difficult. An increase or decrease in heart rate or respiratory rate should be assessed and monitored during treatment.

174.3.1 Box 174-1 Clinical Values for Normal Puppies and Kittens

- *Heart rate:* 200 beats/min (puppy) and 250 beats/min (kitten)
- *Respiratory rate:* 15 breaths/min (birth) and 30 breaths/min (by 1 to 3 hours after birth)
- *Temperature:* 95.4° to 98.6° F at birth, normalizing to adult values at 4 weeks

- *Mean arterial pressure:* 49 mm Hg at 1 month of age, 94 mm Hg at 9 months (puppies)
- *Central venous pressure:* 8 cm H_2O at 1 month of age, 2 cm H_2O at 9 months (puppies)

174.4 LABORATORY VALUES

The hematocrit (Hct) decreases from 47.5% at birth to 29.9% by day 28 in puppies (Box 174-2).[1] By the end of the first month, the Hct starts to increase again. Kittens also have a Hct nadir at 4 to 6 weeks of 27%.[2] Knowledge of this normal decrease in Hct is essential for assessment of any neonate, and during this period a rise in the Hct is usually indicative of dehydration.

Slight changes are seen in the biochemical profile of newborn puppies and kittens. In dogs there is a mild increase in bilirubin (0.5 mg/dl; normal adult range 0 to 0.4) and dramatic increases in serum alkaline phosphatase (3845 IU/L, normal adult range 4 to 107) and γ-glutamyltransferase (1111 IU/L, normal adult range 0 to 7).[3] In kittens, the alkaline phosphatase (123 IU/L, normal adult range 9 to 42) is three-fold higher than that seen in adults.

Lower values of blood urea nitrogen (BUN), creatinine, albumin, cholesterol, and total protein are seen in neonates compared with adults (although the BUN may be slightly elevated during the first week of life). Calcium and phosphorous are higher in neonates. Urine is isosthenuric in neonates because the capacity to concentrate or dilute urine is limited in this age-group.[4] This becomes important in fluid therapy because overhydration is just as much of a concern as underhydration.

174.5 IMAGING

Normal anatomic differences in the young may be significant and are reviewed briefly. The thymus is located in the cranial thorax on the left side and can mimic a mediastinal mass or lung consolidation on thoracic radiographs. The heart takes up more space in the thorax than it does in adults and can appear enlarged. The lung parenchyma has increased water content and appears more opaque in neonates.[5] There is an absence of costochondral mineralization, making the liver appear to protrude further from under the rib cage than expected, making a misdiagnosis of hepatomegaly more likely. There is loss of abdominal detail due to lack of fat and a small amount of abdominal effusion.[5] Radiographic resolution may be improved by reducing the kVp value to half of the adult setting and using detailed film or screens.

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174.5.1 Box 174-2 Laboratory Values for Puppies and Kittens

174.5.1.1 Complete Blood Count—Pediatric Canine

Hematocrit: 47% at birth, 29% at 28 days

Leukocyte count: $12.0 \times 10^3/mm^3$, peaks on day 7

Band count: $0.5 \times 10^3/mm^3$, peaks on day 7

Lymphocyte count: 5 × 10^3/mm^3, peaks on day 7

Eosinophil count: 0.8 × 10^3/mm^3, peaks on day 7

174.5.1.2 Complete Blood Count—Pediatric Feline

Hematocrit: 35% at birth, 27% at 28 days

Leukocyte count: 9.6 × 10^3/mm^3 at birth; 23.68 × 10^3/mm^3 at 8 weeks

Lymphocyte count: 10.17 × 10^3/mm^3 at 8 weeks; 8.7 × 10^3/mm^3 at 16 weeks

Eosinophil count: 2.28 × 10^3/mm^3 at 8 weeks; 1 × 10^3/mm^3 at 16 weeks

174.5.1.3 Biochemistry Profiles—Pediatric Canine*

Bilirubin: 0.5 mg/dl (range, 0.2 to 1; normal adult range, 0 to 0.4)

Alkaline phosphatase: 3845 IU/L (range, 618 to 8760; normal adult range, 4 to 107)

γ-*Glutamyltransferase:* 1111 IU/L (range, 163 to 3558; normal adult range, 0 to 7)

Total protein: 4.1 g/dl (range, 3.4 to 5.2; normal adult range, 5.4 to 7.4)

Albumin: 1.8 g/dl at 2 to 4 weeks (range, 1.7 to 2; normal adult range, 2.1 to 2.3)

Glucose: 88 mg/dl (range, 52 to 127; normal adult range, 65 to 100)

174.5.1.4 Biochemistry Profiles—Pediatric Feline*

Bilirubin: 0.3 mg/dl (range, 0.1 to 1; normal adult range, 0 to 0.2)

Alkaline phosphatase: 123 IU/L (range, 68 to 269; normal adult range, 9 to 42)

γ-*Glutamyltransferase:* 1 IU/L (range, 0 to 3; normal adult range, 0 to 4)

Total protein: 4.4 g/dl (range, 4 to 5.2; normal adult range, 5.8 to 8)

Albumin: 2.1 g/dl (range, 2 to 2.4; normal adult range, 2.3 to 3)

Glucose: 117 mg/dl (range, 76 to 129; normal adult range, 63 to 144)

*At birth except where specified.

174.6 INTRAVENOUS AND INTRAOSSEOUS CATHETERIZATION

When venous access is required, the intravenous route is preferred and should be attempted first. Neonates often require very-small-gauge catheters (e.g., 24 gauge), which can develops burrs easily when driven through the skin. A small skin puncture with a 20-gauge needle (while the skin is kept elevated) can be made, and the catheter is then fed through the skin hole.

If attempts at intravenous catheter placement fail, an intraosseous catheter should be placed (see Chapter 62, Intraosseous Catheterization). An intraosseous catheter can be inserted in the proximal femur or humerus using an 18-gauge to 22-gauge spinal needle or an 18- to 25-gauge hypodermic needle. An intraosseous catheter can be used for fluid and blood administration.[6] The area must be prepared in a sterile manner and the needle inserted into the bone parallel to the long axis. Gentle aspiration will ensures patency, and the bandage is secured with a sterile bandage. Intravenous access must be established as soon as possible, ideally within 2 hours, and the intraosseous catheter should be removed to minimize the risk of osteomyelitis. Intraosseous catheter complications correlate with duration of use.[7]

174.7 FLUID REQUIREMENTS

Neonates have higher fluid requirements than adults because they have a higher percentage of total body water, a greater surface area–to–body weight ratio, a higher metabolic rate, more permeable skin, a decreased renal concentrating ability, and less body fat. Both dehydration and overhydration are concerns because neonatal kidneys cannot concentrate or dilute urine as well as adults can.[4]

A warm isotonic crystalloid bolus (30 to 40 ml/kg in puppies and 20 to 30 ml/kg in kittens) should be administered to moderately dehydrated neonates, followed by a constant rate infusion (CRI) of 80 to 100 ml/kg/day. A liter of fluid warmed to 104° F will cool down to room temperature (70° F) within approximately 10 minutes. A fluid warmer that is placed in-line is a good option. Lactated Ringer's solution may be the ideal fluid because lactate is the preferred metabolic fuel in the neonate with hypoglycemia.[8,9]

Hypoglycemia in neonates commonly occurs as a result of inefficient hepatic gluconeogenesis, inadequate hepatic glycogen stores, and a loss of glucose in the urine. Urinary glucose reabsorption does not normalize until approximately 3 weeks of age in puppies.[10,11] In addition, the neonate has greater glucose requirements than do adults. The neonatal brain requires glucose for energy, and brain damage can occur with prolonged hypoglycemia.[11] Fetal and neonatal myocardia use carbohydrate (glucose) for energy rather than the long-chain fatty acids used by the adult myocardium.[12] In summary, the neonate has an increased demand for, an increased loss of, and a decreased ability to synthesize glucose compared with adults.

In adults, the counter-regulatory hormones are released (i.e., cortisol, growth hormone, glucagon, and epinephrine) in response to low blood glucose levels and facilitate euglycemia by increasing gluconeogenesis and antagonizing insulin. Clinical signs of hypoglycemia can be challenging to recognize in neonates because of inefficient counter-regulatory hormone release during hypoglycemia.[11]

Vomiting, diarrhea, infection, and decreased oral intake all contribute to hypoglycemia in neonates. A bolus of 1 to 2 ml/kg of 12.5% dextrose (i.e., 50% dextrose diluted 1:4 with sterile water) followed by a CRI of isotonic fluids supplemented with 2.5% to 5% dextrose are required to treat hypoglycemia. Any bolus must be followed by a CRI that is supplemented with dextrose, or there is a risk of rebound hypoglycemia. In addition, some neonates may have refractory hypoglycemia and may respond only to hourly boluses of dextrose in addition to a CRI of crystalloids with supplemental dextrose. Carnitine supplementation may allow maximal utilization of glucose and may be considered as an additional therapeutic option. The recommended dosage is 200 to 300 mg/kg PO q24 h for both puppies and kittens. 748 749

The most common causes of hypovolemia in neonates are gastrointestinal (GI) disturbances (e.g., vomiting, anorexia, diarrhea) and inadequate oral intake. The most common cause of diarrhea in neonatal puppies and kittens is iatrogenic (owner) overfeeding with formula. In adults with hypovolemia, compensation occurs by increasing the heart rate, concentrating the urine, and decreasing urine output. In neonates, compensatory mechanisms may not be adequate. Contractile elements make up a smaller portion of the fetal myocardium (30%) compared with the adult myocardium (60%), making it difficult for the fetus to increase cardiac contractility in response to hypovolemia. Neonates also have immature sympathetic nerve fibers in the myocardium and cannot maximally increase heart rate in response to hypovolemia. Complete maturation of the autonomic nervous system does not occur until after 8 weeks in puppies.[13,14] Because neonates have higher fluid requirements and increased losses (less renal concentrating ability, higher respiratory rate, higher metabolic rate), dehydration can progress rapidly to hypovolemia and shock if not adequately treated.

The difficulties associated with assessing hypovolemia in neonates require constant vigilance and continuous monitoring. One must assume that all neonates with severe diarrhea, inadequate intake, or severe vomiting are dehydrated and potentially hypovolemic, and treatment should be initiated immediately. Fluid therapy, monitoring of electrolyte and glucose status, and nutritional support are the mainstays of treatment. The patient should be weighed every 6 to 12 hours. Dehydration is likely when the urine specific gravity reaches 1.020 and this should be monitored as an indicator of rehydration.[15] A bolus of 40 to 45 ml/kg (puppies) or 25 to 30 ml/kg (kittens) of warm isotonic fluids in severely dehydrated or hypovolemic animals is given initially and is followed by a CRI of maintenance fluids (80 to 100 ml/kg/day) and replacement of losses. Losses can be estimated (i.e., two tablespoons of diarrhea is equal to 30 ml of fluid). If the neonate is hypoglycemic or not able to eat, dextrose is added to the intravenous fluids at the lowest concentration that will maintain normoglycemia (i.e., start with 1.25% dextrose).

174.8 TEMPERATURE CONTROL

Neonates are basically poikilothermic for the first 2 weeks of life and are prone to hypothermia because of a greater surface area–to–volume ratio, immature metabolism, immature shivering reflex (develops at 6 days) and vasoconstrictive ability and because their temperature is normally lower than that of mature animals. Hypothermic patients should be rewarmed slowly. Animals that are separated from the mother should be placed in a neonatal incubator at a temperature of 85° to 90° F and humidity of 55% to 65%. Heat lamps or heating pads and hot water bottles may also be used, but the neonate should be able to crawl away from the heat source. Heating pads should be covered with a towel to prevent burns.

174.9 NUTRITION

Nutrition is crucial to neonatal health, and animals with inadequate caloric intake must be addressed promptly to prevent malnutrition. A surrogate dam is ideal if the biologic dam is unavailable, but this is often difficult to arrange. Weighing the neonate on a pediatric gram scale before and after each feeding can help the clinician to monitor intake.

Bottle and tube feeding are other therapeutic options. Animals that are separated from the mother should be stabilized and rewarmed slowly before feeding because hypothermia prevents digestion and induces ileus. A human infant bottle is preferred for puppies because they often cannot latch onto the smaller “kitten” nipple supplied with most replacement formulas. Tube feeding is done using a 5 Fr red rubber catheter for neonates under 300 g and an 8 to 10 Fr for larger neonates and should be performed only by experienced personnel.[16] Improper placement of the feeding tube in the trachea is easily done in neonates because the gag reflex does not develop until 10 days of age.

Up to 10% of body weight may be lost within the first 24 hours following birth; additional weight loss or failure to gain weight is abnormal. Puppies should double their weight within 10 days of birth and gain 5% to 10% of their body weight per day. Nursing kittens should also double their weight within the first 10 days of life, and normal kittens gain 10 to 15 g per day. Formula-fed neonates grow at significantly slower rates, despite identical caloric intake. Although critically ill neonates and pediatric patients may not gain weight normally, weight loss should be prevented.

174.10 MONITORING

Monitoring disease progression and efficacy of treatment can be challenging in neonates because many parameters are significantly different compared with adults. Mean arterial pressure is lower (49 mm Hg at 1 month of age in puppies) and does not normalize (94 mm Hg) until 9 months of age.[17] Central venous pressure is higher (8 cm H_2O) at 1 month of age in puppies but decreases (2 cm H_2O) by 9 months of age[17] (see Box 174-1).

Neonates cannot autoregulate their renal blood pressure with variations in systemic arterial pressure as adults do, causing the glomerular filtration rate to decrease as the systemic blood pressure decreases.[17] This makes restoration of intravenous fluid volume critical in neonates.

Appropriate renal concentration and dilution of urine does not occur until approximately 10 weeks of age.[18,19] Simultaneously, BUN and creatinine are lower in neonates than adults, making monitoring of azotemia very challenging.

The best way to monitor for underhydration or overhydration is to have an accurate pediatric gram scale and weigh the patient 3 to 4 times per day. Baseline thoracic radiographs are also helpful because normal neonate lungs have more interstitial fluid than adult lungs, and it can be difficult to diagnose fluid overload without a baseline. Other ways to monitor fluid therapy include checking Hct and total solids. Bear in mind that the Hct will decrease progressively in normal neonates from day 1 to 28, and total solids are lower than in adults (see Laboratory Values previously).

Neonatal skin has a lower fat and higher water content than does that of adults and, therefore, skin turgor cannot be used to assess dehydration. Mucous membranes remain moist in severely dehydrated neonates and cannot be used for assessment. Lactate, thought to be a good indicator of perfusion, especially when used serially, has been shown to be higher in normal puppies than in adult dogs (1.07 to 6.59 mmol/L at 4 days old and 0.80 to 4.60 mmol/L from 10 to 28 days of age).[20]

Hypothermia is common in neonates (78° to 94° F) and is associated with a depressed respiratory rate, bradycardia, 749
750 GI paralysis, and coma. Rectal temperature should be monitored using a normal digital thermometer. Temperatures above the normothermic range indicate fever or excessive external warming.

174.11 PHARMACOLOGY

Drug metabolism in neonates differs significantly compared with adults because of differences in body fat, total protein, and albumin (a protein to which many drugs bind). Renal clearance of drugs is decreased in neonates and renal excretion of many drugs (e.g., diazepam, digoxin) is diminished, thus increasing the half-life of the drug in circulation.[4] Hepatic clearance is more complicated. Drugs requiring activation via hepatic metabolism will have lower plasma concentrations, and drugs requiring metabolism for excretion will have higher plasma concentrations.[21,22]

The oral route of fluid and drug administration should be avoided during the first 72 hours of life because absorption is significantly higher due to increased GI permeability. Intestinal flora is very sensitive to disruption by oral antimicrobial agents. Intravenous routes seem to be the most predictable and are preferred over intramuscular or subcutaneous routes in this age-group.[4]

One of the safest classes of antibiotics in neonates is the β-lactam group (i.e., penicillins and cephalosporins), but the dosage interval should be increased to every 12 hours rather than every 8 hours.[4] Metronidazole is the preferred drug for giardiasis and anaerobes. The dosage should be decreased or the interval increased in neonates.

Cardiovascular drug dosages (e.g., epinephrine, dopamine, dobutamine) can be quite difficult to determine in neonates because of individual variations in maturity of the autonomic nervous system. Response to treatment and continuous monitoring of hemodynamic variables are essential when using these drugs. Elevations in heart rate after administration of dopamine, dobutamine, or isoproterenol cannot be predicted until 9 to 10 weeks of age, and response to atropine and lidocaine is decreased in the neonate.[23–25] The blood-brain barrier is more permeable in neonates, allowing drugs to enter that do not normally cross over to the central nervous system.[20]

A normal neonatal respiratory rate is about 2 to 3 times higher than that of an adult's as a result of higher airway resistance and higher oxygen demands. Drugs that depress respiration should be avoided in neonates. Neonates are very dependent on a high heart rate to increase cardiac output, so drugs that depress heart rate should be avoided. Opioids are a good choice for analgesia because of their reversibility, but the animal must be monitored closely because of the propensity of these drugs to depress heart and respiratory rate.

174.12 SEPSIS

Wounds, such as tail docking and umbilical cord ligation, or respiratory, urinary, and GI infections are most commonly implicated in neonatal sepsis. Common bacterial isolates include *Staphylococcus, Streptococcus, Escherichia coli, Klebsiella, Enterobacter, Clostridium,* and *Salmonella*. Additional causes of sepsis might include brucellosis, viral infections (distemper, panleukopenia, herpesvirus infection, feline infectious peritonitis, and feline leukemia virus infection), and toxoplasmosis. Clinical signs, as with hypovolemia, are often subtle or absent, making the diagnosis difficult in this age-group. Some clinical signs that may be associated with sepsis include crying and reluctance to nurse, decreased urine output, and cold extremities.

Studies of sepsis in children and several animal models have documented improved survival associated with rapid, aggressive fluid resuscitation.[26] Large volumes of fluid are often needed in septic patients because of their increased capillary permeability (increased losses) and vasodilation. Resuscitation should be started immediately with a bolus of 30 to 45 ml/kg (puppies) and 25 to 30 ml/kg (kittens) of warm isotonic fluids, followed by a reassessment of the parameters of perfusion (see later in this section).

If perfusion has normalized, a CRI consisting of maintenance fluids plus dehydration estimates and ongoing losses is begun. If perfusion has not normalized, repeated boluses may be required. Monitoring includes serial checks of perfusion parameters via mucous membrane color, pulse quality, extremity temperature, lactate levels, and mentation. A CRI of fresh or fresh frozen plasma or subcutaneous administration of serum from a well-vaccinated adult may help to augment immunity.[27] One study in kittens showed that both intraperitoneal and subcutaneous administration of adult cat serum in three 5-ml increments (at birth and 12 and 24 hours) resulted in immunoglobulin G concentrations equivalent to those seen in kittens that suckled normally.[28] Frequent checks of electrolytes, blood glucose, body temperature, and nutrition are done as indicated above.

Septic neonates that have been adequately fluid resuscitated, but that remain in a hypoperfused state (i.e., cold extremities, high lactate levels, low urine output) may benefit from vasopressor or inotropic support, or both (i.e., dopamine, dobutamine, phenylephrine, norepinephrine). Because of variations in the maturity of the autonomic nervous system, all pressor and inotropic drugs need to be tailored to each animal. Acceptable end points of perfusion include increases in extremity temperature, decreases in lactate levels, increased urine production, and improvement in attitude.

Ideally a sample for culture and sensitivity testing from the area of concern will be submitted before beginning antibiotics. Broad-spectrum antibiotics may be required if the source of infection cannot be identified. Penicillins or first-generation cephalosporins are good choices in the neonate.

Oxygen therapy, if needed, should be kept at or below an inspired oxygen fraction of 0.4 to avoid oxygen toxicity, which can cause retrolental fibroplasia and lead to permanent blindness.[29]

Sepsis can be very difficult to detect in neonates. An index of suspicion should be maintained for all neonates with risk factors, and treatment should be instituted rapidly and aggressively. The incidence of pediatric sepsis in humans is highest in premature newborns. Respiratory infections (37%) and primary bacteremia (25%) are the most common infections.[30]

174.13 CONCLUSION

Their unique anatomic and physiologic characteristics make diagnosis, monitoring, and treatment of these critically ill neonatal and pediatric patients challenging. Adult parameters cannot be relied on in very young patients, and an awareness of their unique characteristics is essential. In addition, many laboratory and pharmacologic data differ dramatically in neonates compared with adults of the same species. Familiarity with these variations is essential in the monitoring and treatment of the neonatal or pediatric patient that may be suffering from hypovolemia, shock, or sepsis. 750 751

SUGGESTED FURTHER READING*

DM Boothe, K Tannert: Special considerations for drug and fluid therapy in the pediatric patient. *Comp Cont Educ Pract Vet*. **14**, 1992, 313, *Excellent review of pharmacology and fluid therapy in young animals*.

MA McMichael, GE Lees, J Hennessey, et al.: Serial plasma lactate concentrations in 68 puppies aged 4 to 80 days. *J Vet Emerg Crit Care*. **15**, 2005, 17, *Research paper looking at 68 puppies from the age of 4 days to 80 days and documenting the changes in lactate concentration as they age. Provides reference ranges for lactate in puppies*.

B Partington: The physical examination and diagnostic imaging techniques. In JD Hoskins (Ed.): *Veterinary pediatrics: dogs and cats from birth to six months*. ed 3, 2001, Saunders, Philadelphia, *Review of some of the changes that occur on radiographs of neonates*.

NJ Thomas, JA Carcillo: Hypovolemic shock in pediatric patients. *New Horiz*. **6**, 1998, 120, *Excellent review of diagnosis and treatment of hypovolemic shock in neonatal and pediatric children*.

* See the CD-ROM for a complete list of references.

175 Chapter 175 Critically Geriatric Patients

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175.1 KEY POINTS

- The number of geriatric pet cats and dogs is growing rapidly in the United States and Europe.
- Maintenance energy requirements decrease in older dogs but appear to increase in older (greater than 12 years) cats, affecting nutritional requirements in these age-groups.
- Many parameters are unchanged in the older animal at rest but differ significantly when stressed with illness or chronic disease.
- Older animals do not appear to possess physiologic reserves, and acute illness can significantly tax their organ systems.

175.2 INTRODUCTION

The number of geriatric pets has increased considerably during the last 10 years. In 1995 in the United States the percentage of pet cats over 6 years of age was 24% of the population. Today it is estimated to be approximately 47%.[1] In Europe the number of geriatric cats increased by over 100% between 1983 and 1995, and the number of geriatric dogs increased by approximately 50% during that time.[2] Unfortunately this growing subset of the pet population has received little scientific scrutiny, and research pertaining to geriatric critical care is extremely sparse.

In geriatric people, several studies have shown that older age alone does not predict mortality. The main determinants of mortality are prior health status and severity of current disease process.[3-5] Although these same studies have not been done in veterinary medicine, it seems prudent to offer aggressive treatment to the older dog and cat once comorbid diseases, quality of life for the pet, and the owner's desires are taken into consideration.

The term *geriatric* is difficult to define in veterinary medicine because it differs between dogs and cats and among breeds (e.g., a Great Dane has a much shorter lifespan than a Chihuahua). In general, animals older than 7 years are considered geriatric.

The objective of this chapter is to review the physiologic changes that occur as a result of aging as they relate to critical care medicine.

175.3 LABORATORY VALUES

In people at rest, the laboratory values of red blood cells, white blood cells, platelets, and hemoglobin do not change with age. However, there is a decrease in the ability of the bone marrow to increase neutrophil production in response to infection and to increase red blood cell production in response to anemia in geriatric people.[6] Neutrophil function has also been shown to decrease with age in people.[6]

There are no established reference ranges for geriatric small animal patients, perhaps because the term *geriatric* is difficult to define, and therefore the laboratory values are difficult to quantify. Harper and others looked at age-related variations in laboratory values in Beagles and Labrador Retrievers. The data were grouped into categories, and the geriatric category included all animals over 10 years of age. There were no differences between the dogs greater than 10 years of age and the rest of the adults.[7] Strasser and others[8] looked at age-dependent changes in laboratory values before and after exercise in Beagles. There were no significant differences in the laboratory values between 5-year-old and 10-year-old Beagles at rest. After exercise, however, there were significant differences in many of the parameters. The older dogs had lower hematocrits, red blood cell counts, and hemoglobin concentrations. They also had a significantly lower venous oxygen saturation and lower plasma glucose levels.[8] In addition, older dogs have a slower hematopoietic response to acute anemia (phlebotomy) than younger dogs.[6]

Although there are limited data for older animals, the research suggests that at-rest laboratory values may not be very different between adult and geriatric animals. However, when stressed by exercise, or perhaps by disease, older animals may show significant differences in laboratory values and the disease process may place a large burden on their tenuous reserves.

The coagulation system appears to shift toward hypercoagulability as humans age, and the incidence of pulmonary thromboembolism is increased five-fold in humans older than 85 years.[6] Although changes in this system with age have not been investigated in small animal patients, prophylactic treatment for hypercoagulability may be warranted in this age-group, especially in animals with predisposing disease processes.

The human thoracic cage becomes more rigid and the lungs lose elasticity with age. Respiratory muscle strength is decreased by 25%, and the alveolar-arterial gradient increases significantly.[9] Loss of diaphragmatic and intercostal muscle mass is thought to be responsible for the decline in respiratory muscle strength. These aging changes may result in a decreased arterial partial pressure of oxygen in older veterinary patients, but this is not well documented. Diseases such as pneumonia, pulmonary thromboembolism, and pulmonary edema place great pressure on the limited pulmonary reserves and may be more difficult to treat for these reasons.

Renal blood flow, glomerular filtration rate, urine concentrating and diluting ability, and creatinine clearance have been shown to decrease with age in people.[9] Inability to conserve sodium or concentrate urine and decreased renal blood flow have been reported in geriatric small animals.[10] This combination leads to the inability of the aged to respond to hypovolemia or hypervolemia and often places severe restrictions on fluid and electrolyte therapy.

175.4 IMAGING

Thoracic radiographs of geriatric dogs and cats can show increased lung opacity due to calcification of the bronchial circulation and pulmonary interstitial changes. These can be mistaken for pulmonary disease. The heart may appear to "lie on the sternum" in old cats as it takes on a more horizontal orientation. This can easily be mistaken for cardiomegaly because of increased sternal contact. The aorta may appear more prominent in older cats due to a "kink" in its appearance. The liver may extend beyond the costal arch and appear enlarged in older animals because of stretching of the ligaments that attach it to the diaphragm.

Spondylosis of the vertebrae are common in older dogs, and degenerative joint disease changes may be seen in both species as they age.

175.5 FLUID THERAPY

Significant changes in multiple organ systems in geriatric animals should be taken into account when selecting the type, dosage, and rate of fluids.

Geriatric animals have increasing amounts of myocardial fibrosis, valvular malfunction, and myocardial fiber atrophy.[10] The decrease in ventricular compliance limits the volume that they can tolerate while paradoxically increasing their dependency on volume. Geriatric animals are highly dependent on end-diastolic volume to increase cardiac output and therefore do not tolerate volume depletion very well during times of stress (e.g., illness, anesthesia).

Renal changes, such as the decreased ability to concentrate or dilute urine, decreased renal blood flow, and the limited ability to conserve sodium, all limit the geriatric animal's ability to handle volume depletion, volume overload, or electrolyte disturbances.

Balanced isotonic crystalloids (i.e., lactated Ringer's solution, 0.9% sodium chloride) are ideal for the dehydrated geriatric patient. Both natural (fresh frozen plasma) and artificial colloids (hydroxyethyl starch) are additional options for hypovolemia but should be administered at a slower rate in geriatric animals because of their propensity for volume overload. Supplements such as potassium chloride, vitamin B complex, and dextrose are added as needed.

A thorough search for underlying or chronic disease processes (chronic valvular disease, renal failure) is essential when planning fluid therapy. It is imperative that fluid therapy be monitored both diligently and frequently. Monitoring for optimal perfusion includes frequent checks of pulse quality, extremity temperature, venous lactate levels, urine output, body weight, and mentation. Monitoring for fluid overload includes frequent checks of respiratory rate, thoracic auscultation, body weight, urine output, central venous pressure, arterial blood gases or pulse oximetry, and thoracic radiographs.

175.6 NUTRITION

Maintenance energy requirements decrease with age in dogs but appear to increase after the age of 12 years in cats.[11-13] In addition, there may be a decrease in the ability to digest fat and protein as cats age.[14] These changes can lead to either weight gain (i.e., if an older dog is fed food with the same caloric content as it ages) or weight loss (i.e., if an older cat is fed food with the same caloric content as it ages). The reduced ability to digest fats can lead to deficiencies in fat-soluble vitamins (e.g., vitamin E) along with water-soluble vitamins (e.g., B vitamins) and electrolytes.[14] In older dogs with a limited ability to digest fats due to a diminished ability to secrete pancreatic lipase or bile acids, medium chain triglycerides may be beneficial as a concentrated and highly absorbable energy source.

Adequate protein intake is essential for optimal immune function and is critical in geriatric animals. Protein requirements actually increase in older dogs, and the old dogma recommending protein restriction for kidney protection has been discounted.[15-18]

Antioxidants are essential to combat oxidative stress, which has been shown to increase with age in many species.[19] The free radical/oxidative stress theory of aging suggests that levels of reactive oxygen species increase with age, and amelioration of this increase can retard the aging process.[19] Oxidative stress represents an imbalance

between oxidative damage (i.e., free radical damage) and endogenous antioxidant protection. Antioxidants can be administered exogenously and are thought to contribute to decreased levels of oxidative stress and perhaps to increased quality of aging. Some antioxidants that can be added easily to the treatment regimen include vitamin B 752
complex in the intravenous fluids 753 (4 ml/L when given at a maintenance rate), *S*-adenosyl-L-methionine given orally (20 mg/kg q24h), and N-acetylcysteine given intravenously (50 to 70 mg/kg over 1 hour diluted 1:4 with 0.9% sodium chloride and filtered q6-8h) or orally (50 mg/kg q8-12h). Oral N-acetylcysteine can be found in health food stores in the amino acid section.

Anorexia in the older critically ill patient is common and should be treated aggressively after a thorough search for underlying causes. Intravenous midazolam given to anorectic cats caused eating to begin within 2 minutes, and propofol had a similar effect on anorectic dogs.[20,21] Cat food should be delivered in wide, shallow food bowls to prevent the whiskers from touching the sides. Also, smell is an important appetite stimulant in both dogs and cats, and clogged nasal passages (e.g., from bilateral nasal catheters for the delivery of oxygen) may cause decreased appetite. Warming the food and placing a small amount on the tongue may help stimulate the animal to eat.

175.7 PHARMACOLOGY

Aging imposes several changes in the absorption, distribution, metabolism, and elimination of many drugs.

Oral absorption may be decreased because gastrointestinal function slows as the animal ages. The loss of lean body mass can alter intramuscular drug absorption.

Distribution of drugs may be altered for several reasons. If fluid retention is present (such as with congestive heart failure, cirrhosis, or renal failure), drugs that are distributed to the extracellular space (e.g., penicillins, nonsteroidal antiinflammatory drugs, aminoglycosides) may have changes in their distribution. Albumin, the protein to which many drugs bind, decreases with age.[22]

Drug metabolism may change as the geriatric patient experiences a decline in hepatic function. The mass of the liver decreases with age, causing a decrease in overall hepatic function that could cause an increased plasma half-life of drugs that require hepatic excretion, metabolism, or conjugation.[10] Decreased function of phase I metabolic reactions in the liver appear to occur with age and cause decreases in oxidation, reduction, dealkylation, and hydroxylation reactions. Phase II reactions do not appear to be altered.[23]

Drug elimination may be affected by a progressive decline in renal function with age. In geriatric humans there is a steady decline in renal function, with approximately 40% of the nephrons becoming sclerotic and renal blood flow and glomerular filtration rate decreasing by almost 50% by the age of 85.[6] Because of the loss of lean body mass, creatinine levels may remain normal (decreased production and decreased clearance). Approximately 15% to 20% of dogs and cats are thought to suffer from some degree of renal insufficiency as they enter the geriatric years.[24]

There is a progressive decline in the number of cardiac myocytes and in ventricular compliance in geriatric humans. Autonomic tissue is replaced by fat and connective tissue and shows decreased responsiveness to autonomic drugs.[6] It is likely that some decline in cardiac function occurs with age in animals, and careful monitoring for specific end points is essential when prescribing cardiac drugs.

Options for appropriate drug dosing in geriatric animals include measurement of renal function, therapeutic drug monitoring with frequent dosage adjustments, and dosage or interval reduction according to creatinine concentrations. The most practical and cost efficient of these options is dosage or interval reduction. Dosage and interval adjustments based on creatinine use the following formulas:

$$\text{Adjusted dosage} = \text{normal dosage} \times (\text{normal serum creatinine} \div \text{patient's serum creatinine}) \quad \text{or}$$

$$\text{Adjusted interval} = \text{normal interval} \; (1 \div [\text{normal serum creatinine} \div \text{patient's serum creatinine}])$$

It is essential to take any comorbid diseases (e.g., congestive heart failure, chronic renal failure, hepatic fibrosis) into account in considering dosage adjustments for geriatric small animals. For example if a dog with chronic renal insufficiency requires therapy with angiotensin-converting enzyme inhibitors, the clinician must be aware of the significant likelihood of decreased renal clearance in this animal as a result of both its chronic renal disease and older age.

For a good review of general guidelines for dosage adjustments in geriatric small animals, see the article by Dowling and colleagues.[22]

175.8 CONCLUSION

Geriatric animals experience a decline of physiologic reserves that may not be apparent at rest. During times of ill health, however, when needed to meet the demands of the disease process, the geriatric animal often cannot mobilize reserves and the illness may result in multiple organ failure.

Because of changes in cardiovascular, renal, hepatic, nutritional, and immune function, the older animal will respond differently to both the stress of illness and its treatment than will the young adult. It is essential that the critical care team be familiar with these changes in the older animal and be prepared for vigilant monitoring during diagnostic testing and treatment of the illness.

The severity of illness has the biggest influence on outcome in critically ill geriatric people, and this is likely to be similar in animals. Aggressive and appropriate treatment, careful monitoring, and, of course, tender loving care are essential to a successful outcome in the critically ill geriatric patient.

175.9 SUGGESTED FURTHER READING*

RE Carpenter, GR Pettifer, WJ Tranquilli: Anesthesia for geriatric patients. *Vet Clin North Am Small Anim Pract*. **35**, 2005, 571, *Excellent review of anesthesia for geriatric small animal patients*.

PM Dowling: Geriatric pharmacology. *Vet Clin North Am Small Anim Pract*. **35**, 2005, 557, *Excellent review of geriatric pharmacology in small animals*.

W Kraft: Geriatrics in canine and feline internal medicine. *Eur J Med Res*. **3**, 1998, 31–41, *Review of statistics for European dog and cat populations*.

DP Laflamme: Nutrition for aging cats and dogs and the importance of body condition. *Vet Clin North Am Small Anim Pract*. **35**, 2005, 713, *Excellent review of nutritional requirement changes that occur as dogs and cats age*.

M Stratton-Phelps: AAFP and AFM panel report of feline senior health care. *Comp Cont Educ Pract Vet*. **21**, 1999, 531, *Review of statistics for U.S. feline population*.

* See the CD-ROM for a complete list of references.

176 Chapter 176 Vasoactive Catecholamines

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176.1 KEY POINTS

- Naturally occurring catecholamines include dopamine, epinephrine, and norepinephrine. They share a common synthesis pathway and are formed most commonly in the sympathetic nervous system or the adrenal medulla.
- Catecholamines function by activating adrenergic receptors. The type of receptors (α or β) stimulated determines the function of the catecholamine.
- In the cardiovascular system, alpha receptor stimulation induces vasoconstriction. Beta receptor stimulation increases heart rate, enhances cardiac contractility, and causes peripheral vasodilation.
- Dobutamine is typically the preferred β-agonist in dogs. Because seizures may result from dobutamine administration to cats, dopamine may be preferable in this species.
- Norepinephrine may be the preferred α-agonist, although dopamine may be equally effective.
- If the clinician unsure whether a β-agonist or α-agonist is required, the former is typically the safest first choice.

176.2 INTRODUCTION

The use of vasoactive catecholamines is common in the therapeutic management of cardiovascularly unstable, critically ill patients. Proper use of these medications requires accurate understanding of their functions and effects. This knowledge begins with the understanding of in vivo catecholamine physiology and the function of the adrenergic receptors. Understanding the chemical properties of the adrenergic agonists, as well as the basis for their use, is also necessary to complete the foundation of knowledge for this subject.

176.3 PHYSIOLOGY OF CATECHOLAMINES

176.3.1 Catecholamine Synthesis

Catecholamines are neurotransmitters when they are produced in the sympathetic nervous system and brain and circulating hormones when synthesized in the adrenal medulla. The endogenous catecholamines include dopamine, epinephrine, and norepinephrine. The specific compound formed depends on the enzymes produced by the synthesizing tissue. All three of these catecholamines are synthesized in a similar fashion, beginning with tyrosine. The first and rate-limiting step in the production pathway is the conversion of tyrosine to L-dopa by tyrosine hydroxylase.[1,2] L-dopa is converted to dopamine through the action of dopa decarboxylase. If dopaminergic receptors are the target, this is where the pathway stops.

However, if adrenergic receptors are the target of catecholamine synthesis, then conversion of dopamine to norepinephrine follows. Depending on the tissue type and species, norepinephrine may be converted to epinephrine. For instance, in the adrenal medulla of dogs and humans, most (80%) of the product synthesized is epinephrine. In cats, however, norepinephrine is the major product.[3] When produced in the adrenal medulla, the catecholamine is then released into the blood. When synthesized in the sympathetic nervous system, release occurs near the effector cell from the axon.

176.3.2 Catecholamine Receptors

The effects of catecholamines are based more on their receptor profile than on the specific catecholamine. Adrenergic receptors are highly specific prosthetic groups on membrane proteins found on the effector cell. The function of the receptors depends on the effector organ, but can be generally divided into two main actions: (1) causing a change in the cell membrane permeability to one or more ions and (2) activating or inactivating an enzyme attached to the receptor.[2] The most common ions affected are sodium, calcium, and potassium. Sodium and calcium typically depolarize the cell for excitation, whereas potassium usually exits the cell making the cell more electronegative. Activation or inactivation of an enzyme in a cell can cause many different effects depending on the enzyme and the cell type. One of the most common enzymes associated with these receptors is cyclic adenosine monophosphate (cAMP).[2]

Adrenergic receptors are typically divided into alpha_1, alpha_2, beta_1, and beta_2 receptors. The various catecholamines are not equal in their abilities to stimulate all receptors. Norepinephrine stimulates α-receptors more than β-receptors, and epinephrine stimulates both receptor types equally. Thus norepinephrine is not as effective as epinephrine in activating organs with predominantly β-receptors.

176.3.3 Catecholamine Effects

As previously discussed, the effects of catecholamines depend on the distribution, type, and action of the receptors. α-Receptors or β-receptors can be either excitatory or inhibitory. Actions of α-receptors include vasoconstriction, iris dilation, intestinal relaxation, and bladder sphincter contraction. α_1-Receptor agonists cause vasodilation or vasoconstriction depending on the concentration and the specific vascular beds. α_2-Agonists are pure vasoconstrictors, whereas the β-receptors are more dependent on the subtype. β_1-Receptors cause increased heart rate, cardiac contractility, renin release, and lipolysis. The β_2-receptors cause vasodilation, intestinal relaxation, bronchodilation, glycogenolysis, and bladder relaxation.

Thus specific receptor agonist drugs can be administered to achieve a desired effect. For instance, to treat hypotension due to a loss of systemic vascular resistance, an α-agonist may be superior to a beta drug or a nonspecific agonist. 756 757 Meanwhile, managing hypotension caused by a decrease in cardiac function would be best accomplished using a β_1-agonist.

Table 176-1 Dosages and Receptor Activity of Adrenergic Drugs

Drug	Alpha Activity	Beta Activity	Dosage (μg/kg/min)	Comments
Dobutamine	+	β_1+++, β_2++	2 to 20 (dogs) 1 to 5 (cats)	May cause seizures in cats
Dopamine (low dosage)	0 to +	0 to +	1 to 4	Vasodilation via dopaminergic receptors
Dopamine (medium dosage)	+ to ++	+ to +++	5 to 10	Inconsistent plasma levels
Dopamine (high dosage)	+++	+ to +++	10 to 20	Inconsistent plasma levels
Epinephrine	+++	++ to +++	0.005 to 1	Significant side effects
Isoproterenol	0 to +	β_1++, β_2+++	0.04 to 0.08	Reserved for heart block
Norepinephrine	+++	+ to ++	0.05 to 2	Primarily an alpha agonist
Phenylephrine	+++	0 to +	1 to 3	Significant side effects

176.4 SPECIFIC CATECHOLAMINES

See Table 176-1 for dosages of all discussed drugs.

176.4.1 β-Adrenergic Drugs

176.4.1.1 Dobutamine

Dobutamine is a synthetic β-adrenergic agent that more strongly stimulates β_1-receptors than β_2-receptors. The overall effect is a strong increase in cardiac contractility but little change in heart rate and systemic vascular resistance.[4] Dobutamine is typically useful for low cardiac output states in patients with adequate intravascular volume. Common side effects include arrhythmias, tachycardia, and vasodilation. In cats, higher dosages (>5 μg/kg/min) may induce central nervous system (CNS) signs such as seizures or tremors.

176.4.1.2 Dopamine

Dopamine is the precursor to norepinephrine, but it also has adrenergic effects that are related to the dosage used. The lowest dosage (1 to 4 μg/kg/min) activates the dopamine receptors in healthy patients. There are two major types of dopamine receptors, D_1 and D_2 receptors. These receptors typically are targeted with dopaminergic drugs during oliguric renal failure (this use is controversial), hypertension, or fulminant pulmonary edema. Activation of these receptors causes splanchnic vasodilation, natriuresis, diuresis, and variable alterations in renal and gastrointestinal (GI) blood flow.[5]

At midrange dosages (5 to 10 μg/kg/min) dopamine stimulates β-adrenergic receptors and, to a lesser degree, α-receptors. The expected net effect is an increase in cardiac contractility and heart rate with a mild increase in systemic vascular resistance. Although the plasma levels of dopamine are consistent in healthy patients, there has been significant variability noted in critically ill patients.[6] Thus the dose-response relationship of dopamine is theoretical; the effects of dopamine in critically ill patients can be extremely variable. High-dose dopamine therapy is discussed in the next section, α-Adrenergic Drugs.

Potential side effects of dopamine include arrhythmias, tachycardia, and increased systemic vascular resistance. Another possible side effect in critically ill humans is a decrease in the partial pressure of oxygen in arterial blood.[7] This effect presumably results from an increase in cardiac output and pulmonary arterial vasoconstriction. In addition, redistribution of GI and renal blood flow secondary to dopamine receptor activation may increase the susceptibility of these organs to ischemia.[5,7]

176.4.1.3 Epinephrine

Epinephrine has comparable beta and alpha effects, although lower dosages are associated with increases in cardiac output with minimal changes in systemic vascular resistance. The overall effect is an increase in heart rate, contractility, and systemic vascular resistance. Most negative effects are associated with severe vasoconstriction and a significant increase in oxygen consumption that accompanies the increase in oxygen delivery. This effect can cause an increase in sensitivity to hypoxia in certain tissues such as cardiac muscle, the GI tract, kidneys, and liver. The inability to select for β-receptor or α-receptor effects make epinephrine generally a poor choice except in resistant hypotension or cardiopulmonary cerebral resuscitation.[7]

176.4.1.4 Isoproterenol

Isoproterenol, a nonspecific β-agonist is a potent inotrope and chronotrope. Beta stimulation may also cause a decrease in systemic vascular resistance. The major effect of isoproterenol administration is an increase in the rates of the sinoatrial node, atrioventricular node, and ventricles. Accordingly, isoproterenol is most commonly used for the treatment of patients with third-degree heart block. Side effects include arrhythmias, tachycardia, and hypotension.[4]

176.4.2 α-Adrenergic Drugs

176.4.2.1 Dopamine

Higher dosages of dopamine (10 to 20 μg/kg/min) primarily activate the α-adrenergic receptors. Dopamine is considered an effective α-agonist. However, the same concerns as noted in the previous section on dopamine exist. Furthermore, there is evidence that dopamine has more negative effects than norepinephrine.[7,8] These include a possible increase in renal, gastrointestinal, and cardiac ischemia.

176.4.2.2 Epinephrine

See the previous section.

176.4.2.3 Norepinephrine

Norepinephrine has significant α-adrenergic receptor mediated effects with less beta activation. The overall effect is an increase in systemic vascular resistance with little increase in heart rate. The increase in cardiac contractility is variable. Recent research indicates that norepinephrine increases blood flow to the heart and kidneys without significant ischemia to other tissues.[10] This action would potentially make norepinephrine superior to the other α-adrenergic agonists.[7,9]

176.4.2.4 Phenylephrine

Phenylephrine is a pure α-agonist. Significant vasoconstriction is the net effect of administration. Secondarily, a reflex bradycardia is common. The vasoconstriction can cause excessive decreases in blood flow to the GI tract, liver, and kidneys, although coronary blood flow is increased.[4] At higher dosages, some β-adrenergic effects can be seen.

176.5 SUGGESTED GUIDELINES FOR USE

Choosing the appropriate catecholamine for cardiovascular support can be difficult. This difficulty is often due to the veterinarian's inability to determine the type and degree of adrenergic receptor stimulation that would be most beneficial. Without information derived from a pulmonary artery catheter and an arterial catheter placement, it is often difficult to identify whether poor cardiac function, poor vascular volume, and/or poor vascular tone is the primary source of a patient's cardiovascular instability (see Chapter 6, Hypotension).

Catecholamines are rarely warranted in cases with inadequate intravascular volume. Evaluating intravascular volume may be difficult, although central venous pressures may facilitate the assessment (see Chapters 63, 65, and 203, Central Venous Catheterization, Shock Fluids and Fluid Challenge, and Hemodynamic Monitoring, respectively). The choice between an α-adrenergic agonist or β-adrenergic agonist administration is considered after patients have failed to respond to intravascular volume expansion.

Typically, β-adrenergic agonists are used to manage refractory systemic hypotension, cardiogenic shock (except hypertrophic cardiomyopathy), severe pulmonary edema, low-output congestive heart failure, and oliguric renal failure in patients with adequate intravascular volume.[4,7] Because of the significant negative effects associated with increasing afterload through vasoconstriction, a primary β-agonist is often a prudent first choice when considering catecholamine therapy. The use of afterload-increasing α-agonist drugs is potentially dangerous in animals with diseases such as dilated cardiomyopathy and mitral valve regurgitation because a decrease in cardiac output will result. When considering the β-agonists, the choice between dobutamine and dopamine is still debated. The uncertainty remains because of a lack of clinical trials to determine effectiveness and safety of these drugs in veterinary medicine. Human clinical trials have led to consensus statements that dobutamine is the preferred choice in severe sepsis and septic shock.[9] Until similar trials are conducted in veterinary patients, the choice remains empiric or extrapolated from human medicine.

Whichever β-agonist is administered, the recommended method is to initiate a low dosage and titrate up every 15 to 20 minutes by 25% increments until the desired effect is reached. This desired effect depends upon the reason for initiating management, such as clinically significant hypotension, resistant lactic acidosis, and/or oliguria.

If the desired effect is not attained with a β-agonist or inappropriate clinical signs of vasodilation are present despite hypotension, then α-agonist therapy should be considered. As with the β-agonists, no clear preferable α-agonist has been documented in clinical trials. Both dopamine and norepinephrine are considered preferred choices, although once again some work suggests that norepinephrine may be a better choice.[10] Phenylephrine, although very potent, may have more severe side effects and is generally reserved for cases that are refractory to other α-agonists.

As with the β-agonists, the α-agonists are initiated at the lowest dosage and incrementally increased to the desired effect. The goal with all catecholamines is to use the lowest dosage necessary for the shortest time possible to achieve the target end point. Due to their short half life, catecholamines lose their effectiveness minutes after single dosage administration and are therefore more commonly delivered as constant rate infusions.[1,2] Also, these drugs tend to become less effective after several days of continuous infusion due to downregulation of adrenergic receptors.[1]

176.6 CONCLUSION

Catecholamines should be used with an understanding of their function and adverse effects. Catecholamines should never replace appropriate therapy of the underlying disease. Furthermore, adequate intravascular volume expansion should precede their use. When unsure whether decreased cardiac contractility or vasodilation is the underlying cause of hypotension, the safest first choice is usually a β-agonist such as dobutamine. Although no clear best choice of β-agonist or α-agonist exists, extrapolation from clinical trials in human medicine suggests that dobutamine and norepinephrine are preferable.

176.7 SUGGESTED FURTHER READING*

NJ Laste: Cardiovascular pharmacotherapy. In N Dhupa (Ed.): *The Veterinary Clinics of North America: small animal practice*. 2001, Saunders, Philadelphia, *Edition of* Veterinary Clinics of North America *covering cardiovascular critical care issues, including hypotension and vasoactive catecholamines*.

E McNiel, BD Husbands: Pheochromocytoma. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2005, Saunders, St Louis, *Chapter that focuses on adrenergic physiology and pathophysiology of dogs and cats*.

* See the CD-ROM for a complete list of references

177 Chapter 177 Vasopressin

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177.1 KEY POINTS

- Vasopressin, also known as *antidiuretic hormone,* is a peptide hormone synthesized in the hypothalamus and stored or released from the posterior pituitary gland.
- There are four vasopressin receptors in the body: V_1R, V_2R, V_3R, and the oxytocin receptor.
- In health, vasopressin aids in the regulation of free water balance (via V_2R) in the renal medullary and cortical collecting ducts.
- During states of circulatory shock, vasopressin levels are markedly increased, and vasopressin functions as a potent nonadrenergic vasoconstrictor (via V_1R). Vasopressin also stimulates the release of adrenocorticotropic hormone (V_3R).
- Vasopressin is used therapeutically for the management of pituitary-dependent diabetes insipidus, von Willebrand disease, vasodilatory hypotension, and cardiopulmonary resuscitation.

177.2 PHYSIOLOGY OF VASOPRESSIN

Arginine vasopressin (AVP, also known as *antidiuretic hormone [ADH], 8-arginine-vasopressin,* or *β-hypophamine*) is a natural, nine amino acid glycopeptide with a disulfide bond that is synthesized in the magnocellular neurons in the hypothalamus before transport down the pituitary stalk for storage in the pars nervosa of the posterior pituitary gland.[1] The entire process of vasopressin synthesis, transport, and storage in the pituitary takes 1 to 2 hours.

AVP is metabolized rapidly by hepatic and renal vasopressinases, and the half-life of AVP is 10 to 35 minutes. Vasopressin has shown teleologic persistence and is found in more than 120 species spanning four invertebrate phyla and the seven major vertebrate families.[2] In most mammals (dogs, cats, humans), the natural hormone is AVP, but the porcine species has a lysine in place of arginine, rendering the compound less potent than AVP.

The most potent stimuli for AVP release are increased plasma osmolality, decreased blood pressure, and a decrease in circulating blood volume.[3-5] Additional abnormalities that cause AVP release include pain, nausea, hypoxia, hypercarbia, pharyngeal stimuli, glycopenia, drugs or chemicals (i.e., acetylcholine, high-dose opioids, dopamine, angiotensin II, prostaglandins, glutamine, histamine), certain malignant tumors, and mechanical ventilation.[6-8]

Release of AVP is inhibited by drugs such as glucocorticoids, low-dose opioids, atrial natriuretic factor, and γ-aminobutyric acid. Hyperosmolality is sensed by both peripheral and central osmoreceptors. Central osmoreceptors are located outside the blood-brain barrier and detect changes in systemic osmolality. Peripheral osmoreceptors in the hepatic portal veins enable early detection of the osmolality of ingested food and liquids. Afferent impulses ascend via the vagus nerve to the paraventricular and supraoptic nuclei within the blood-brain barrier to stimulate its release. In addition, plasma hypertonicity depolarizes the magnocellular neurons of the hypothalamus to cause more AVP release.

Table 177-1 Vasopressin Receptors, Tissues Affected, and Principal Effects

Receptors	Tissues	Principal Effects
V_1R (V_{1a})	Vascular smooth muscle	Vasoconstriction at high doses Vasodilation in cerebral, renal, pulmonary, and mesenteric vessels at low dosages
V_2R	Renal collecting duct	Increased water permeability
	Platelets	Stimulate aggregation
V_3R (V_{1b})	Pituitary	ACTH release
OTR	Uterus, mammary gland, GI tract Endothelium	Contraction Vasodilation

ACTH, Adrenocorticotropic hormone; *GI,* gastrointestinal; *OTR,* oxytocin receptor.

Decreases in blood volume or pressure also stimulate exponential increases in AVP. Hypovolemia and hypotension shift the osmolality-vasopressin response curve so that higher vasopressin levels are required to maintain a normal osmolality in hypotensive states.[9] Afferent impulses from the left atrial, aortic arch, and carotid sinus stretch receptors tonically inhibit vasopressin secretion. Atrial stretch receptors respond to increases in blood volume, and the receptors in the aortic arch and carotid sinuses respond to increases in arterial blood pressure. A decrease in arterial baroreceptor activity increases vasopressin secretion during hypotensive states.

177.3 VASOPRESSIN RECEPTORS

Vasopressin receptors are G protein–coupled receptors. The cellular effects of vasopressin are mediated by interactions of the hormone with several types of receptors (Table 177-1). V_1 receptors (V_1R), previously known as V_{1a} receptors, are found primarily on vascular smooth muscle cells and cause vasoconstriction in most vascular beds that is mediated by G_q protein–coupled activation of the phospholipase C and phosphoinositide pathways. Increased levels of inositol phosphate and diacylglycerol activate voltage-gated calcium channels. This results in increased intracellular calcium levels and subsequent vasoconstriction.

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Vasopressin also causes inactivation of the potassium–adenosine triphosphate channels in vascular smooth muscle cells. Opening of these channels (as occurs with acidosis or hypoxia) allows an efflux of potassium from the endothelial cells, subsequent hyperpolarization, and prevention of calcium from entering the cells. (An increase in cytosolic calcium is essential for vasoconstriction.) In contrast, inactivation of the potassium–adenosine triphosphate channel leads to depolarization, opening of the voltage-gated calcium channels, and an increase in cytosolic calcium with subsequent vasoconstriction.

Interestingly, vasodilation may occur in some vascular beds, most likely mediated by nitric oxide. V_1Rs are found in the vascular endothelium of the kidney, skin, skeletal muscle, pancreas, thyroid gland, myometrium, bladder, hepatocytes, adipocytes, and spleen. Platelets also express the V_1R, which causes an increase in intracellular calcium and facilitates thrombosis when stimulated. V_1Rs in the kidneys lead to reduced blood flow to the inner medulla, limit the antidiuretic effects of vasopressin, and selectively cause contraction of the efferent arterioles to increase glomerular filtration rate. There is considerable variation among species with respect to the location and function of the V_1R.

V_2 receptors (V_2Rs) are found primarily on the basolateral membrane of the distal tubule and in the principal cells of the cortical and medullary renal collecting duct. Coupling of the V_2R with the G_s signaling pathway increases intracellular cAMP. The cAMP triggers fusion of the aquaporin-2–bearing vesicles with the apical plasma membrane of the collecting duct principal cells to increase free water absorption. AVP regulates water homeostasis in two ways: (1) regulation of the fast shuttling of aquaporin-2 to the cell surface and (2) stimulation of the synthesis of messenger ribonucleic acid–encoding aquaporin-2. Most animals with nephrogenic diabetes insipidus have V_2R gene mutations.

V_2R activation also stimulates the release of platelets from the bone marrow and enhances the release of von Willebrand factor and factor VIII from endothelial cells. It causes a mild increase in the activity of factor VIII–related antigen and ristocetin cofactor. There may also be V_2Rs in the vascular endothelium, because the potent V_2R agonist 1-deamino-8-D-arginine vasopressin (DDAVP) causes vasodilation in addition to the release of von Willebrand factor and factor VIII.

The V_3 pituitary receptors (V_3R, previously known as $V_{1b}R$) activate G_q protein and release intracellular calcium after activation of phospholipase C and the phosphoinositol cascade. V_3R activation stimulates release of adrenocorticotropic hormone from the anterior pituitary gland.[10] These receptors are also responsible for the actions of vasopressin on the central nervous system, where they act as a neurotransmitter or a modulator of memory, blood pressure, body temperature, sleep cycles, and release of pituitary hormones.

The oxytocin receptor is a nonselective vasopressin receptor with equal affinity for both AVP and oxytocin. Activation of the oxytocin receptor leads to smooth muscle contraction, primarily in the myometrium and mammary myoepithelial cells. AVP also acts on oxytocin receptors in the umbilical vein, aorta, and pulmonary artery, where it causes a nitric oxide–mediated vasodilation. Stimulation of cardiac oxytocin receptors leads to the release of atrial natriuretic peptide.

Vasopressin also stimulates the P_2 class of purinoreceptors (ATP receptors), which leads to vasodilation mediated by nitric oxide and prostacyclin. P_2 receptors are also positive inotropic agents without direct effects on heart rate.

177.4 PHYSIOLOGIC EFFECTS OF VASOPRESSIN

Vasopressin causes direct systemic vasoconstriction via the V_1Rs. In vitro, vasopressin is a more potent vasoconstrictor than angiotensin II, norepinephrine, or phenylephrine on a molar basis. It is vital for osmoregulation and maintenance of normovolemia, mediated by the V_2Rs. In addition, AVP maintains hemostasis and assists with temperature modulation, memory, sleep, and secretion of adrenocorticotropic hormone. During normal physiologic states, AVP's primary role is the regulation of free water balance. Vasopressin levels in fasting humans is less than 4 pg/ml. Small increases in plasma osmolality lead to an increase in AVP to 10 pg/ml. A maximum increase in urine osmolality is seen with AVP levels greater than 20 pg/ml.

Vasopressin does not control vascular smooth muscle constriction in normal animals, but it is vital in states of hypotension.[10-12] Plasma AVP levels of 50 pg/ml must be attained before a significant increase in arterial pressure is achieved in humans. The pressor (vasoconstrictive) effects of vasopressin are nonadrenergic and thought to be mediated by its direct and indirect effects on arterial smooth muscle. Stimulation of the V_1R leads to vasoconstriction of the skin, skeletal muscles, fat, bladder, myometrium, liver, spleen, pancreas, and thyroid gland. Low levels of vasopressin lead to vasodilation in the cerebral, pulmonary, mesenteric, and renal vessels.[13] Even with potent stimuli for release, only 10% to 20% of the vasopressin stored in the pituitary can be readily released, and further release occurs at a much slower rate that results in a biphasic response to vasodilatory shock.[14]

177.5 PHARMACOLOGY

Exogenous vasopressin (8-arginine vasopressin) is sold as a sterile aqueous solution of synthetic vasopressin for intravenous, intramuscular, or subcutaneous administration. It is destroyed within the gastrointestinal (GI) tract and should only be given parenterally. It is not protein bound, has a volume of distribution of 140 ml/kg, and a half-life of approximately 24 minutes. The drug is cleared by renal excretion (65%) and metabolism by tissue peptidases (35%). Terlipressin (triglycyl-lysine vasopressin) is a prodrug that is converted to lysine vasopressin in the circulation and has a prolonged duration of action, with an effective half-life of approximately 6 hours. To the author's knowledge, this form of vasopressin has not been used clinically in veterinary medicine.

Desmopressin acetate is a synthetic vasopressin analog that is available as both an intranasal and injectable form. (An oral tablet form is also manufactured, but the bioavailability following oral ingestion is very low.) It has more potent antidiuretic and procoagulant activity and less vasopressor action than vasopressin on a per weight basis. Both formulations of the drug should be stored in the refrigerator (although the nasal formulation is stable at room temperature for 3 weeks).

Desmopressin acetate causes a dosage-dependent increase in plasma factor VIII and plasminogen factor. It also causes smaller increases in factor VIII–related antigen and ristocetin cofactor activities, but the effect is sustained for only 3 to 4 hours. The onset of antidiuretic action in dogs usually occurs within 2 hour of administration, peaks in 2 to 8 hours, and may persist for up to 24 hours. The metabolism of desmopressin is not well understood. The terminal half-life in humans after intravenous administration ranges from 0.4 to 4 hours.

177.6 CLINICAL USES

See Table 177-2.

177.6.1 Cardiopulmonary Resuscitation

The use of AVP to manage cardiac arrest has been studied extensively in laboratory animals, and a meta analysis found that AVP was at least equivalent to epinephrine in its ability to aid in the return of spontaneous circulation or survival in humans.[15] Experimental cardiopulmonary resuscitation studies in pigs showed that AVP improved cerebral oxygen delivery, resuscitation success, neurologic outcome, and blood flow to major organs, when compared with epinephrine. Vasopressin has been added to the 2000 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care for the treatment of unstable ventricular tachycardia and ventricular fibrillation. In a large human study comparing AVP with epinephrine, there was a significant increase in survival for following asystolic arrest in humans who were given AVP.[16]

Vasopressin levels are elevated following cardiopulmonary arrest, and levels are significantly higher in humans who are resuscitated than in patients that do not survive.[17] There is one published case of a dog with intraoperative asystolic cardiac arrest that was successfully resuscitated with 2 doses of 0.8 IU/kg AVP IV (atropine and defibrillation were also necessary),[18] but additional clinical evidence is anecdotal. Vasopressin has a lower duration of effect and produces a greater vasoconstrictive effect during hypoxic and acidemic episodes of cardiopulmonary arrest than does epinephrine. In normal experimental animals, the half-life of vasopressin is 10 to 20 minutes.[19] Extrapolated doses in dogs are 0.4 to 0.8 IU/kg IV, with a constant rate infusion of 1 to 4 mU/kg/min, if needed. Endobronchial administration has been studied in pigs. A systematic review and metaanalysis has been published.[15]

Table 177-2 Indications and Dosages for Vasopressin Therapy

Indication	Dosage
Cardiopulmonary resuscitation	0.4 to 0.8 IU/kg IV ± 1 to 4 mU/kg/min IV CRI (dogs)*
Vasodilatory shock	0.5 to 2 mU/kg/min IV CRI (dogs)*
Central diabetes insipidus	0.1 mg/ml Intranasal solution: 1 to 4 drops of into conjunctival sac q12-24h or 0.01 to 0.05 ml SC q12-24h Alternatively, aqueous AVP may be used at 3 to 5 IU/dog or 0.5 IU/kg (cat) SC q4h or as needed
von Willebrand disease	1 to 4 μg/kg DDAVP SC q3-4h (dogs)
Gastrointestinal disease	Unknown

AVP, Arginine vasopressin; *CRI,* constant rate infusion; *DDAVP,* 1-deamino-8-D-arginine vasopressin; *IV,* intravenous; *SC,* subcutaneous.

* Extrapolated from human dosage; dosage in cats is unknown.

177.6.2 Vasodilatory Shock

Vasopressin deficiency can play an important role in animals with vasoplegia secondary to sepsis, prolonged hemorrhagic shock, or cardiac arrest. Experimentally, exogenous AVP infusions to yield plasma AVP concentrations of 20 to 30 pg/ml can restore blood pressure with minimal adverse effects on organ perfusion. Low-flow states secondary to hypovolemia or septic shock are associated with a biphasic response in serum vasopressin levels. There is an early increase in the release of vasopressin from the neurohypophysis in response to hypoxia, hypotension, or acidosis that leads to high levels of serum vasopressin. This plays a role in the stabilization of arterial pressure and organ perfusion in the initial stages of shock. Agents that block the V_1R lower arterial pressure in both acute hemorrhagic shock and septic shock.

Previous studies in dogs have found concentrations of vasopressin in the range of 300 to 1000 pg/ml during the early phase of hemorrhagic shock and 500 to 1200 pg/ml following experimentally induced endotoxemia (further details later in this chapter). During the later phase of shock, however, the vasopressin levels are decreased, presumably a result of degradation of released vasopressin and a depletion of the neurohypophyseal stores that take time to resynthesize. The vasopressin concentration in the experimental dogs decreased to 29 pg/ml during the late phase of hemorrhagic shock.

Humans with advanced vasodilatory shock have both a deficiency of vasopressin secretion and an enhanced sensitivity to vasopressin-induced blood pressure changes. Additionally, vasopressin levels are markedly increased in animal models of acute sepsis, but this increase is followed by a rapid decline over the ensuing few hours. Additional hypotheses for the low levels of vasopressin include a decrease in baroreceptor stimulation of vasopressin in hypotensive patients release secondary to impaired autonomic reflexes, as seen in sepsis, or tonic inhibition by atrial stretch receptors secondary to volume loading or mechanical ventilation. In addition, vasopressin release may be inhibited by nitric oxide or high circulating levels of norepinephrine.

Several human studies and reports have demonstrated promising results for the treatment of people with refractory hypotension using a vasopressin intravenous infusion. Many human patients were subsequently weaned off of catecholamine support by the addition of vasopressin therapy. In addition, there is an increase in urine output, presumably secondary to an increase in renal perfusion pressure due to renal efferent arteriolar constriction. Humans who received AVP therapy before their dosages of norepinephrine exceeded 0.5 μg/kg/min had an improved outcome.[20]

Animal trials thus far support the potential benefits of vasopressin in animals suffering from hypotensive states. However, high-dose therapy is associated with excessive coronary and splanchnic vasoconstriction, as well as a hypercoagulable state. The excessive vasoconstriction can lead to a reduction in cardiac output or even fatal cardiac events, especially in patients with decreased myocardial function.

Guzman and colleagues[21] compared the effects of intravenous norepinephrine with those of intravenous vasopressin on systemic splanchnic and renal circulation in anesthetized dogs with experimentally induced endotoxic shock. Except for a more pronounced bradycardia in the vasopressin group, the systemic and splanchnic blood flow changes were comparable. However, the vasopressin infusion restored renal blood flow and oxygen delivery, but the norepinephrine therapy did not. These types of studies are not representing patients that have catecholamine-resistant hypotension, but the end-organ results are expected to be similar.

Another canine study by Morales and associates[22] studied the effect of vasopressin administration in dogs with experimental hemorrhagic shock and subsequent requirement for a norepinephrine infusion (3 μg/kg/min) to maintain a mean arterial pressure of 40 mm Hg. A vasopressin infusion resulted in an increase in mean arterial pressures from 39 ± 6 mm Hg to 128 ± 9 mm Hg. The serum vasopressin levels were markedly elevated during the acute hemorrhage but decreased from 319 ± 66 to 29 ± 9 pg/ml before administration of vasopressin.

Clinically, vasopressin has been used in dogs with refractory vasodilatory shock.[23] A dosage of 0.5 mU/kg/min was administered intravenously and titrated higher as needed to achieve a mean arterial pressure over 70 mm Hg and heart rate less than 140 beats/min. There was a significant increase in mean arterial pressure with minimal side effects. The mean dosage used was 2.1 mU/kg/min. There is no information regarding survival because all of the clinical dogs were euthanatized or died.

177.6.3 Central Diabetes Insipidus

Animals with central diabetes insipidus and subsequent deficiency of endogenous vasopressin will benefit from treatment with either aqueous vasopressin or DDAVP. Caution should be exercised to prevent water intoxication, and serial electrolytes should be analyzed during treatment. DDAVP is often preferred because it has more antidiuretic activity and less potential vasopressor properties on a per weight basis. One to four drops of the 0.1 mg/ml intranasal solution is typically given into the conjunctival sac once or twice daily. Alternatively, subcutaneous doses of 0.01 to 0.05 ml are used in dogs once to twice daily. Aqueous vasopressin has been administered using doses of using 3 to 5 IU/dog or 0.5 IU/kg in cats SC q4h or as needed (see Chapter 70, Diabetes Insipidus).

177.6.4 von Willebrand Disease

Vasopressin or DDAVP may be useful in von Willebrand disease, except for those animals with type IIB or platelet-type (pseudo) forms, because platelet aggregation and thrombocytopenia may occur. In addition, treatment with DDAVP or vasopressin often is confounded by their short duration of activity (2 to 4 hours), development of resistance, and expense. It is not effective for dogs with severe type II and III von Willebrand disease. Dosage is 1 to 4 μg/kg of DDAVP SC q3-4h. Onset of activity is typically within 30 minutes, and effects lasts approximately 2 hours (see Chapter 118, Bleeding Disorders).

177.6.5 Gastrointestinal Disease

Several uses of AVP in humans have not yet been studied in dogs. These include the acute treatment of esophageal varices and hemorrhagic gastroenteritis, stimulation of peristalsis in patients with postoperative ileus, and dispelling of intestinal gas before abdominal imaging.

177.7 SIDE EFFECTS

AVP can cause contraction of the bladder and gallbladder smooth muscle and can increase peristalsis (especially of the colon). The drug may decrease gastric secretions and increase GI sphincter pressure. Potential adverse effects of AVP administration include local irritation at the injection site, skin necrosis if extravasated, and skin reactions. Humans treated with AVP for vasodilatory shock have developed an increase in liver enzyme and bilirubin levels, decrease in platelet count, hyponatremia, anaphylaxis, bronchospasm, abdominal pain, hematuria, and urticaria, although the incidence of side effects appears to be quite low. Theoretically, because AVP causes a release of von Willebrand factor, it enhances platelet aggregation and may increase the risk of thrombosis. Water intoxication has been reported with high dose therapy for the treatment of diabetes insipidus. Vasopressin or DDAVP may cause irritation when administered in the conjunctival sac.

177.8 CONCLUSIONS

Vasopressin is a drug with many actions, several receptors, and multiple therapeutic uses. It is important to understand the mechanisms of action of the various receptors and the mechanisms of action of the various formulations to treat animals safely and appropriately. The use of this drug in veterinary medicine is expanding as research in people and experimental models continues.

177.9 SUGGESTED FURTHER READING*

K Aung, T Htay: Vasopressin for cardiac arrest: a systematic review and meta-analysis. *Arch Intern Med*. **165**, 2005, 17, *A systematic review and meta-analysis of 1519 human patients with cardiac arrest from five randomized controlled trials that compared vasopressin and epinephrine. Provides results that did not show a clear advantage with vasopressin, but that it is at least equivalent to epinephrine*.

JA Guzman, AE Rosado, JA Kruse: Vasopressin vs norepinephrine in endotoxic shock: systemic, renal, and splanchnic hemodynamic and oxygen transport effects. *J Appl Physiol*. **95**, 2003, 803, *A nicely done study comparing the effects of norepinephrine and vasopressin on systemic, splanchnic, and renal circulations in anesthetized dogs under basal conditions and with endotoxic shock. Restoration of renal blood flow and oxygen delivery in the vasopressin, but not the norepinephrine group, and the systemic and splanchnic hemodynamic comparable between the two groups*.

CL Holmes, DW Landry, JT Granton: Science review: vasopressin and the cardiovascular system: Part I. Receptor physiology. *Crit Care*. **7**, 2003, 427, *An excellent review of the vasopressin receptors*.

CL Holmes, DW Landry, JT Granton: Science review: vasopressin and the cardiovascular system: Part II. Clinical physiology. *Crit Care*. **8**, 2004, 15, *A great review of AVP and adrenergic agonists' effects on* *smooth muscle physiology, cardiac inotropy, and coronary perfusion, and clinical studies up to the date of the paper's publication*.

CL Holmes, BM Patel, JA Russell, et al.: Physiology of vasopressin relevant to management of septic shock. *Chest*. **120**, 2001, 989, *An excellent review of vasopressin, especially the physiology of vasopressin relevant to septic shock*.

PC Kam, S Williams, FF Yoong: Vasopressin and terlipressin: pharmacology and its clinical relevance. *Anaesthesia*. **59**, 2004, 993, *An article that nicely reviews the physiology and pharmacology of vasopressin and summarizes its efficacy and safety in clinical trials and its subsequent therapeutic use*.

* See the CD-ROM for a complete list of references

178 Chapter 178 Antihypertensives

Mary Anna Labato, DVM, DACVIM

178.1 KEY POINTS

- Hypertension is divided into two categories: primary and secondary.
- Primary hypertension results from an imbalance between cardiac output and systemic vascular resistance and is usually idiopathic.
- Secondary hypertension accounts for almost all identified cases of elevated blood pressure in veterinary medicine.
- Normal blood pressure values are not identical for dogs and cats. Normal values for dogs are breed specific to some degree.
- Overall, canine average blood pressure (systolic/diastolic) is 133/75 mm Hg.
- Overall, feline average blood pressure (systolic/diastolic) is 124/84 mm Hg.
- Blood pressure values higher than 160/95 mm Hg on three separate occasions are consistent with hypertension.
- There are a number of classes of substances used for antihypertensive therapy, and often multiple modalities are required.
- Angiotensin-converting enzyme inhibitors and calcium channel blockers are the most commonly used antihypertensive agents employed in veterinary medicine.

178.2 INTRODUCTION

The definition of normal blood pressure in dogs and cats has been quite elusive and remains the subject of significant research, debate, and confusion.[1] It has been demonstrated that normal values for dogs appeared to be somewhat breed specific, but for cats they are not.[2]

The definition of hypertension has been lowered. At this time it is thought that blood pressure values higher than 150/95 mm Hg on three separate visits in a patient that demonstrates no clinical signs are compatible with hypertension, as is a single reading higher than 150/95 mm Hg in a patient with evidence of clinical disease in organs susceptible to end-organ damage.[1,3]

178.3 ETIOLOGY

Patients are classified as having primary (essential) or secondary hypertension. In the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for Humans (JNC7), a third category termed *prehypertension* was established.[4]

Prehypertension describes blood pressures ranging from 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic, or both. This new designation is intended to identify those individuals in whom early intervention (changing to a healthy lifestyle and diet) could reduce blood pressure or decrease the rate of increase in blood pressure to hypertensive levels.[4]

Primary hypertension is the result of an imbalance in the relationship between cardiac output and systemic vascular resistance. The exact cause is not known. There is little known about the prevalence of primary hypertension in animals. There have been reports of both dogs and cats with primary hypertension when secondary causes could not be determined.[5-7]

Secondary hypertension is defined as elevated blood pressure that results from systemic disease or medication. Secondary hypertension accounts for almost all identified cases of elevated blood pressure in veterinary patients. The following disorders are associated with a significant risk of developing hypertension: renal disease, diabetes mellitus, hyperadrenocorticism, thyroid disease, and hepatic disease. Additionally, more uncommon causes include pheochromocytoma, hyperaldosteronism, polycythemia, and chronic anemia. Drugs such as erythropoietin and glucocorticoids have also been associated with elevations in blood pressure.[8-16]

178.4 PROPOSED MECHANISM OF BLOOD PRESSURE ELEVATION

A number of diseases and a variety of hypotheses have been associated with elevations in blood pressure. In patients with hyperadrenocorticism, glucocorticoids induce hepatic production of angiotensinogen, resulting in an exaggerated response of the renin-angiotensin system.[8] The hypertension that develops in animals with hyperthyroidism is secondary to the increased cardiac output secondary to the effect of thyroid hormone on cardiac muscle.[12]

The mechanism by which renal disease results in hypertension is not completely understood. It has been hypothesized that increased blood volume secondary to either a maladaptive increase in renin secretion or inability of the kidneys to process fluids and electrolytes properly may lead to increased venous return of blood to the heart.[11] Increased levels of endogenous vasoconstrictors such as endothelin, thromboxane, and adrenergic stimuli combined with decreased levels of endogenous vasodilators such as prostacyclin and nitric oxide may also be contributing factors.

The mechanism by which hepatic disease results in hypertension is undetermined. In animals with diabetes mellitus, there are possibly four different mechanisms. In humans with type 1 diabetes, hypertension is thought to develop secondary to the effects of diabetes on renal function. With type 2 diabetes, three different mechanisms have been proposed.[14] One is that hyperinsulinemia secondary to insulin resistance causes sodium and water
retention and increased sympathetic activity. This leads to increased peripheral resistance via changes in blood 763
volume and vasoconstriction, respectively. The second proposed mechanism is that hypertrophy of vascular smooth 764
muscle occurs secondary to the mitogenic effects of insulin. The last mechanism is that elevations in insulin levels may lead to increased intracellular calcium. The increased calcium results in hyperresponsive vascular smooth muscle contraction and increased peripheral vascular resistance.

Table 178-1 Summary of Antihypertensive Drugs

Drug	Effect	Indications
Angiotensin-converting enzyme inhibitors Benazepril, enalapril	Arterial and venous vasodilation Decrease preload Decrease afterload	Hypertension Heart failure Proteinuria
Calcium channel antagonists Amlodipine	Arterial vasodilation	Hypertension Hypertensive crisis
β-Adrenergic antagonists Propranolol, atenolol	Decrease cardiac output Decrease sympathetic outflow Decrease blood pressure Cardiodepressant Nonselective (β_1 and β_2) Cardioselective (β_1)	Hypertension Hypertrophic cardiomyopathy Arrhythmias Pheochromocytoma
α-Adrenergic antagonists Prazosin	Balanced vasodilation	Hypertension Pheochromocytoma
Arteriolar vasodilator Hydralazine	Nonspecific arterial vasodilation Reduced peripheral vascular resistance Reduced blood pressure	Hypertension Hypertensive crisis
Arteriolar vasodilator Sodium nitroprusside	Nitric oxide donor Vasodilation	Hypertensive crisis
Angiotensin II receptor blocker Losartan, irbesartan	Arterial and venous vasodilation	Hypertension
Aldosterone blockers Spironolactone, eplerenone	Vasodilation	Hypertension Proteinuria
Dopamine-1 agonist Fenoldopam	Vasodilation Decrease blood pressure Natriuresis Increase in renal blood flow	Hypertension Hypertensive crisis Acute renal failure

Chromocytomas release epinephrine and norepinephrine, resulting in vasoconstriction and increased cardiac output (see Chapter 74, Pheochromocytoma).[15] Administration of erythropoietin has been associated with the development of hypertension. Anemia leads to chronically dilated capillary beds. With resolution of the anemia, overcompensation of capillary constriction occurs, with a resultant increase in peripheral vascular resistance.[16]

178.5 ANTIHYPERTENSIVE DRUGS

178.5.1 Angiotensin-Converting Enzyme Inhibitors

178.5.1.1 Mechanism of Action

Angiotensin-converting enzyme (ACE) inhibitors are often the initial to treatment of choice to control hypertension. ACE inhibitors competitively inhibit the conversion of angiotensin I to angiotensin II. Angiotensin II is one of the most powerful endogenous vasoconstrictors; its inhibition results in systemic vasodilation (Table 178-1).

The primary effects of ACE inhibitors result in a decrease in angiotensin I and II, as well as an increase in bradykinin. Drugs in this class induce arterial and venous vasodilation. Because angiotensin II directly stimulates the kidneys to retain sodium, its inhibition results in a reduced plasma volume. In addition, ACE inhibitors inhibit aldosterone release, leading to a decrease in sodium and water retention and decreased blood volume. There is a reduction in both preload and afterload. The other beneficial effect of ACE inhibitors is that they reduce intraglomerular pressure and inhibit growth factors that lead to glomerular hypertrophy and sclerosis.[1,17-22]

178.5.1.2 Indications

ACE inhibitors are used to reduced blood pressure in all forms of hypertension. They are also used frequently to decrease preload and afterload and inhibit growth factors in patients with mitral insufficiency or congestive heart failure in conjunction with dilated cardiomyopathy. ACE inhibitors reduce proteinuria by maintaining the heparan sulfate layer of the glomerular basement membrane and decreasing.

Although there are a number of ACE inhibitors, the ones used most commonly in veterinary medicine are enalapril, benazepril, ramipril, and lisinopril (Table 178-2). The effects of ACE inhibitors in cats are less predictable. As many as 50% of hypertensive cats do not respond to enalapril, although benazepril has statistically significant antihypertensive effect in cats with renal failure.[1]

178.5.1.3 Side Effects

ACE inhibitors are relatively safe drugs. Side effects include weakness and lethargy attributable to a drop in blood pressure. Reversible increases in blood urea nitrogen and creatinine may result from the decrease in a reduction in renal function (reversible elevation of creatinine and blood urea nitrogen, and decrease in glomerular filtration rate). These effects are especially likely if used in conjunction with diuretics. Hyperkalemia frequently occurs secondary to aldosterone inhibition. A rare side effect is a dry cough induced by bradykinin.

Table 178-2 Commonly Used Antihypertensives and Their Dosages

Drug	Class	Canine Dosage	Feline Dosage
Amlodipine	Calcium channel blocker	0.05 to 0.2 mg/kg PO or PR q24h	0.625 to 1.25 mg PO or PR q24h
Atenolol	β-Adrenergic blocker	0.25 to 1 mg/kg PO q12-24h	6.25 to 12.5 mg PO q12-24h
Benazepril	ACE inhibitor	0.25 to 0.5 mg/kg PO q12-24h	0.25 to 0.5 mg/kg PO q12-24h
Enalapril	ACE inhibitor	0.5 to 1 mg/kg PO q12-24h	0.25 to 0.5 mg/kg PO q12-24h
Enalaprilat	ACE inhibitor	0.1 to 1 mg IV q6h	To be determined
Propranolol	β-Adrenergic blocker	0.04 to 0.1 mg/kg IV q8h or 0.5 to 1 mg/kg PO q8-12h	0.02 to 0.06 mg/kg IV q8-12h*or*0.2 to 1 mg/kg PO q8-12h
Prazosin	α-Adrenergic blocker	0.5 to 2 mg PO q8-12h	0.25 to 0.5 mg/cat PO q24h
Spironolactone	Aldosterone inhibitor	1 to 2 mg/kg PO q12h	1 mg/kg PO q12h
Hydralazine	Arterial vasodilator	0.25 to 4 mg/kg SC or IM q8-12h or 0.1 to 0.2 mg/kg/hr IV CRI*	0.25 to 2 mg/kg SC q8-12h or IM
Sodium nitroprusside	Nonspecific vasodilator	1 to 3 μg/kg/min IV CRI	1 to 2 μg/kg/min IV CRI
Losartan	Angiotensin II receptor blocker	To be determined	To be determined
Lisinopril	ACE inhibitor	0.75 mg/kg PO q24h	0.25 mg/kg PO q24h
Fenoldopam	Dopamine-1 agonist	0.1 to 0.6 μg/kg/min IV CRI	0.1 to 0.6 μg/kg/min IV CRI
Nicardipine	Calcium channel blocker	0.5 to 5 μg/kg/min IV CRI	To be determined
Ramipril	ACE inhibitor	0.125 to 0.25 mg/kg PO q24h	To be determined

ACE, Angiotensin-converting enzyme; *CRI,* constant rate infusion; IM, intramuscular; *IV,* intravenous; *PO,* per os; *PR,* per rectum; SC, subcutaneous.

* Monitor for side effects and titrate slowly.

178.5.2 Angiotensin II Receptor Blockers

178.5.2.1 Mechanism of Action

Angiotensin II receptor blockers (ARBs) are well tolerated, safe, and effective for blood pressure control in humans. Several studies have shown that this class of drugs confers renal benefits in humans with diabetic nephropathy. It is controversial whether ARBs are better at protecting the kidney than ACE inhibitors in patients with type II diabetes mellitus.[19]

ARBs displace angiotensin II from its specific angiotensin I receptor, antagonizing all of its known effects (vasoconstriction, sympathetic activation, aldosterone release, renal sodium resorption) and resulting in a dosage-dependent fall in peripheral vascular resistance with little change in heart rate or cardiac output.[23]

178.5.2.2 Indications

In humans, ARBs are used to treat hypertension and cardiovascular disease. Their efficacy for hypertension in dogs and cats is not known. The drugs losartan and irbesartan have been used in dogs, but more investigation into their role in the veterinary armamentarium needs to be performed.

178.5.2.3 Side Effects

This class of drugs appears to be safe with few side effects. In humans virtually every trial of ARBs given to hypertensive patients shows that they are better tolerated than other classes of antihypertensive medications.[23]

178.5.3 Adrenergic Receptor Antagonists

Drugs that may be useful in the therapy of hypertension are those that block activation of α-adrenergic or β-adrenergic receptors. Propranolol, a β_1 and β_2 adrenergic receptor antagonist; atenolol, a β_1 selective antagonist; and prazosin, an α_1-adrenergic receptor antagonist have been used to manage hypertension in dogs and cats.

The mechanism of action of β-adrenergic blocking agents includes blockade of renin release, reduced heart rate and contractility, a decrease in peripheral vascular resistance, and reduced central adrenergic drive.[1,23]

α-Adrenergic blockers exert their antihypertensive effects by selectively antagonizing α-adrenergic receptors on systemic vessels. Prazosin acts as a competitive antagonist of postsynaptic α_1-receptors. It blocks the activation of the postsynaptic α_1-receptors by circulating or by neurally released catecholamines, an activation that normally induces vasoconstriction. Peripheral resistance falls with minimal changes in cardiac output.[1,23]

178.5.3.1 Indications

β-Adrenergic blockers are useful in dogs and cats when primary antihypertensive treatment fails to produce the desired decrease in blood pressure. They are also used to manage hypertrophic cardiomyopathy and supraventricular and ventricular tachycardias.

α-Adrenergic antagonists have been used for primary or adjunctive therapy for hypertension in dogs. However, these agents have found greater use in micturition disorders, as smooth muscle relaxants of the urethra, and for treatment of hypertension associated with pheochromocytoma.

178.5.3.2 Side Effects

Nonselective β-adrenergic blockers, such as propranolol, should not be used in asthmatic cats because they may induce bronchospasm. Additional side effects include hyperkalemia, bradycardia, insulin resistance, and depression. Some of these side effects occur because the antagonists are not selective for β-receptors or α-receptors.

Prazosin and other α-adrenergic antagonists selectively block vascular α_1-receptors and may cause severe hypotension that is unresponsive to α_1-agonist therapy.

178.5.4 Aldosterone Blockers

The aldosterone antagonist, spironolactone, blocks the effects of aldosterone on the renal distal convoluted tubule and collecting duct and thereby decreases sodium reabsorption and potassium excretion. Its antihypertensive effects, in addition to being a weak diuretic, is through its effect on the renin-angiotensin-aldosterone system. It is useful in treating hyperaldosteronism, iatrogenic steroid edema, refractory edema, and in conjunction with other diuretics.

Eplerenone is a novel agent that antagonizes the aldosterone receptor. It has been associated with severe hyperkalemia, so potassium levels need to be monitored closely. Its major advantage over the nonselective aldosterone receptor antagonist, spironolactone, is the lack of binding to progesterone and androgen receptors. It has been approved for treatment of hypertension in humans. Aldosterone blockers also have been shown experimentally to reduce proteinuria and attenuate renal injury by decreasing renal fibrosis and decreasing inflammation.[24,25]

178.5.4.1 Side Effects

Hyperkalemia may occur with either spironolactone or eplerenone but is not common in the absence of renal insufficiency or concomitant β-blocker, ACE inhibitor, ARB therapy, or potassium supplements.

178.5.5 Calcium Channel Blockers

178.5.5.1 Mechanism of Action

Calcium channel blockers (CCBs) act by blocking the influx of calcium in vascular smooth muscle cells that is necessary to cause smooth muscle contraction, thereby decreasing systemic vascular resistance.[17] These drugs inhibit the slow transmembrane calcium influx into the cell via voltage-gated L-type calcium channels.[26]

The selectivity of the vascular and cardiac effects of the various CCBs varies. Those that cause vasodilation at arterioles and coronary arteries lead to a reduction of peripheral resistance and a reduction in blood pressure. Those that have negative chronotropic, negative dromotropic, and negative inotropic effects lead to antiarrhythmic and cardiodepressant effects.[18]

The dihydropyridines (amlodipine, nicardipine, nifedipine, nimodipine, nitrendipine) are the family of CCBs that primarily act on blood vessels.[18] They are vascular smooth muscle relaxers (arteries, arterioles, and coronary arteries) and exert minimal direct effect on the heart. Dihydropyridines may produce arterial vasodilation and reflex tachycardia.

178.5.5.2 Indications

The indications for CCBs are hypertension and hypertensive crisis. Amlodipine is considered the drug of choice to treat hypertension in cats with chronic renal disease. Amlodipine is long acting, allowing for once-daily dosing, and has a gradual effect that prevents rapid reductions in blood pressure. In animals that cannot tolerate oral medications, rectal amlodipine administration has been used, although the pharmacokinetic data are lacking.

178.5.5.3 Side Effects

Side effects noted with CCB are tachycardia, nausea, constipation, and weakness. There is concern about using a CCB as a primary antihypertensive agent. CCBs were thought to have renoprotective effects equivalent to those of the ACE inhibitors. However, studies have shown that the afferent arteriolar vasodilation is greater than on the efferent arteriolar side of the glomerulus, and this decrease in perfusion pressure may actually decrease glomerular filtration and, at higher dosages, lead to renal damage.[1,17,26]

178.5.6 Arteriolar Vasodilators

178.5.6.1 Hydralazine

178.5.6.1.1 Mechanism of Action

Hydralazine is an arteriolar dilator that acts directly on the smooth muscle of arterioles by incompletely understood mechanisms, resulting in reduced peripheral vascular resistance and reduced blood pressure. Although not a first-choice antihypertensive drug for patients with chronic renal disease, hydralazine has been used to treat hypertension in dogs and cats, especially in cases of hypertensive crisis. Sodium retention and reflex tachycardia may occur. Hydralazine has been known to act as an antioxidant, inhibiting vascular production of reactive oxygen species.[23] Hydralazine may induce arteriolar vasodilation by preventing oxidation of nitric oxide and thereby lower blood pressure.[23]

178.5.6.1.2 Side Effects

In humans three kinds of side effects are seen. The first kind is due to a reflex sympathetic activation. The second type involves a lupus-like reaction. The third kind is nonspecific problems such as anorexia, nausea, vomiting, diarrhea, muscle cramps, and tremor. In veterinary medicine, side effects have primarily been a reflex tachycardia, weakness, and gastrointestinal upset.

178.5.6.2 Sodium Nitroprusside

178.5.6.2.1 Mechanism of Action

Sodium nitroprusside is a nonspecific vasodilator that is a potent antihypertensive agent that brings about immediate relaxation of resistance and capacitance vessels. This is the result of the release of nitric oxide, which stimulates the production of cyclic guanine monophosphate (cGMP) in the vascular smooth muscle. cGMP activates a kinase that subsequently leads to the inhibition of calcium influx into the smooth muscle cell and decreased calcium-calmodulin stimulation of myosin light chain kinase. This in turn decreases the phosphorylation of myosin light chains, thereby decreasing smooth muscle tension and causing vasodilation. Sodium nitroprusside induces minimal change in renal blood flow and only a slight increase in heart rate. It is indicated for a hypertensive crisis, a rapid reduction of preload and afterload in acute heart failure, and controlled blood pressure reduction during surgery. Because of its high potency, it should be used only if blood pressure can be monitored closely.[1,18,23,27,28]

178.5.6.2.2 Side Effects

Shock and severe hypotension may occur. Cyanide intoxication may be seen in patients with reduced hepatic function or if nitroprusside is used for prolonged periods or at high dosages.

178.5.7 Fenoldopam

178.5.7.1 Mechanism of Action

Fenoldopam is a peripheral dopamine-1 agonist and a parenteral antihypertensive agent. It maintains or increases renal perfusion while it lowers blood pressure. Most of its efficacy is maintained for 48 hours of constant rate infusion (CRI), without rebound hypertension when discontinued.[27,28] There is a paucity of data on the use of fenoldopam in clinical veterinary patients, most likely due to the cost of this drug.

178.5.7.2 Indications

The indications for fenoldopam are severe hypertension and hypertensive crisis. It may also be useful in the treatment and prevention of certain forms of acute renal failure.[28]

178.5.7.3 Side Effects

Side effects include reflex tachycardia and increased intraocular pressure. In humans, headache and flushing are also reported.[28]

178.6 HYPERTENSIVE URGENCY

A hypertensive urgency exists when there is a marked elevation in blood pressure but the animal does not demonstrate clinical signs directly attributed to the elevation. The patient is in danger of developing end-organ damage or a vascular accident such as hemorrhage or intravascular coagulation. In these animals it is imperative that blood pressure be lowered, but it should be done in a gradual and controlled fashion.

178.6.1 Treatment of Hypertensive Urgency

Most identified cases of hypertension in veterinary medicine are secondary to other disease processes. The first course of action is to determine the predisposing cause and to institute appropriate therapy. In addition to treating the underlying disease, an antihypertensive drug protocol needs to be incorporated in most patients. An important principle in treating hypertension is to allow 1 to 2 weeks before evaluating the efficacy of a particular drug or dosage adjustment.[1] The therapeutic goal is not to normalize blood pressure, but rather to lower systolic blood pressure to 170 mm Hg or less.

178.7 HYPERTENSIVE EMERGENCY

A hypertensive emergency occurs when the animal has a marked elevation in blood pressure with clinical signs directly attributable to hypertension. These patients should be treated quickly and require monitoring in a critical care facility.[8,17] The JNC7 recommends that the initial goal of therapy in hypertensive emergencies is to reduce mean arterial blood pressure by no more than 25% (within minutes to 1 hour) and then, if stable, to 160/100 to 160/110 mm Hg within the next 2 to 6 hours. Excessive falls in pressure that may precipitate renal, cerebral, or coronary ischemia should be prevented.[4]

178.7.1 Treatment of Hypertensive Emergency

Hypertensive emergencies should be treated at facilities that provide 24-hour critical care. Continuous blood pressure monitoring is imperative. Potentially dangerous medications such as nitroprusside and hydralazine may be used. Sodium nitroprusside is a potent arterial and venous dilator that may begin to act within seconds and has a half-life of 2 to 3 minutes. It needs to be administered as a CRI. Hydralazine is a rapid arteriolar dilator with an unpredictable nature and has been associated with episodes of profound hypotension.[1]

Enalaprilat is a parenteral ACE inhibitor, similar in action to enalapril except that it is fast acting. It is used in hypertensive emergencies. The dosage in human medicine is 0.625 to 1.25 mg IV over 5 minutes q6h. The dosage has been extrapolated for use in veterinary medicine, and the author use 0.1 to 1.0 mg q6h IV.[28]

178.8 SUGGESTED FURTHER READING*

MJ Acierno, MA Labato: Hypertension in dogs and cats. *Comp Cont Educ Pract Vet*. **26**, 2004, 336, *A review article that provides an overview of the causes of hypertension, measurement of blood pressure, and various treatment options*.

SA Brown, CA Brown, G Jacobs, et al.: Effects of the angiotensin converting enzyme inhibitor benazepril in cats with induced renal insufficiency. *Am J Vet Res*. **62**, 2001, 375, *Article that presents a study evaluating the use of benazepril in cats with induced kidney disease. Work that supports the concept that the drug may be an effective therapy*.

SA Brown, RA Henik: Diagnosis and treatment of systemic hypertension. *Vet Clin North Am Small Anim Pract*. **28**, 1998, 1481, *A review of the diagnosis and treatment of systemic hypertension in dogs and cats*.

V Chetboul, HP Lefebvre, C Pinhas, et al.: Spontaneous feline hypertension: clinical and echocardiographic abnormalities, and survival rate. *J Vet Intern Med*. **17**, 2003, 89, *An article that reports on findings in 58 cats with systemic hypertension*.

AV Chobanian, GL Barkus, HR Black, et al.: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. **42**, 2003, 1206, *A comprehensive report on the prevention, evaluation, and treatment of high blood pressure in humans*.

B Egner: Blood pressure measurement. In B Egner, A Carr, S Brown (Eds.): *Essential facts of blood pressure in dogs and cats*. ed 3, 2003, Beate Egner Vet Verlag, Babenhauser, Germany, *A detailed discussion of blood pressure measurement*.

* See the CD-ROM for a complete list of references

179 Chapter 179 Nitroglycerin

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179.1 KEY POINTS

- The most common uses of nitrates in the critical care setting are transdermal nitroglycerin (NTG) and intravenous nitroprusside for acute congestive heart failure (CHF). Transdermal nitrates have a slower onset of activity and primarily affect the venous system. Nitroprusside is a potent arterial and venous dilator and should be used only when arterial blood pressure can be monitored.
- NTG is one of the most effective drugs to ameliorate pain in humans with angina pectoris. Although this use is not commonly needed in animals (as far as we know), nitrates have other beneficial effects that make them important therapy in CHF, especially acute CHF.
- NTG was first known as an explosive and retains that characteristic even today. Modulations of compounds prevent it from being dangerous in medical practice.
- Although patients develop tolerance rapidly to nitrates, this is not true of intravenous nitroprusside. However, nitroprusside can cause cyanide or thiocyanate toxicity, and its use should be limited to 48 hours of a constant rate infusion.
- If an animal cannot tolerate angiotensin-converting enzyme (ACE) inhibitors, the combination of oral NTG and hydralazine is as effective as enalapril in controlling clinical signs of CHF, although they do not have the benefit of the lowered mortality associated with ACE inhibitors.

179.2 INTRODUCTION

Nitroglycerin (NTG) is probably one of the most interesting drugs in the history of medicine because of its use as an explosive before its use as therapy for angina pectoris (chest pain) and as a vasodilator for congestive heart failure (CHF). Who in their right mind would have knowingly placed even a small amount of a known explosive on the tongue? Yet NTG has become the most universally prescribed and recognized treatments for angina pectoris,[1] one of the most commonly diagnosed diseases in humans who live in developed nations.[2]

179.3 PHARMACOLOGY OF NITRATES

As a group, nitrates are absorbed from the skin, the mucous membranes, and the gastrointestinal tract.[2] The common preparations include an oral tablet, a transdermal paste or patch, a sublingual spray or tablet, or a powder that is reconstituted and administered intravenously.[2,3]

NTG relaxes vascular smooth muscle primarily on the venous side and is therefore a preload reducer, although nitroprusside (the intravenous form) can also dilate arteries and is therefore used for severe hypertension or left-sided CHF.[3] NTG is oxidized to nitric oxide (NO), a short-lived free radical that stimulates the production of cyclic guanosine monophosphate (cGMP). cGMP reduces cytosolic calcium by inhibiting flow into the cell while stimulating mitochondrial uptake, causing relaxation of smooth muscle cells.[4]

179.3.1 Tolerance

An important characteristic of NTG administration is tolerance, the loss of efficacy within a short time. Several hypotheses have been proposed to explain this.

179.3.1.1 Impaired Conversion of Nitrates to Nitric Oxide

The enzyme aldehyde dehydrogenase, which participates in the early steps of NO production, may function poorly. In support of this theory is the fact that nitroprusside, a spontaneous NO donor, is less subject to tolerance. This defect is also associated with the production of free radicals.[2,4]

179.3.1.2 Abnormalities in Signal Transduction

This mechanism works by either (1) decreasing the bioavailability of the second messenger cGMP or (2) impairing its effects.

Decreased bioavailability might be mediated by either decreased levels of guanylyl cyclase, the enzyme responsible for the formation of cGMP, or by increased activity of phosphodiesterase (PDE), the enzyme that breaks down cGMP. This latter mechanism explains why excessive lowering of blood pressure may occur when nitrates are combined with certain PDE inhibitors such as sildenafil.[2]

Finally, cGMP activity is impaired when the effects of cGMP-dependent protein kinase, which mediates vasorelaxation, are reduced.[4]

179.3.1.3 Free Radical Formation

There seem to be multiple sources for superoxide anion, which produces toxic peroxynitrite, which ultimately causes decreased formation of vasodilatory cGMP. This may the reason that vitamin C and hydralazine, acting as antioxidants, can lessen nitrate tolerance.[2,4]

179.3.1.4 Neurohumoral Hypothesis

The neurohormones angiotensin II and endothelin can cause stimulation of vasoconstrictive free radicals.[5] Another mechanism is sympathetically induced reflex arterial vasoconstriction in response to marked vasodilation. Renal perfusion is decreased, activating the renin-angiotensin-aldosterone system, thereby increasing angiotensin II. Secondary evidence for the contribution of angiotensin II is the lessening of nitrate tolerance by both ACE inhibitors and angiotensin receptor blockers.[2,5]

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179.3.1.5 Vascular Sulfhydryl Depletion

One of the oldest hypotheses may be outdated. Intracellular formation of NO requires sulfhydryl groups, but excess NO formation depletes intracellular sulfhydryl groups.[2]

179.4 NITROPRUSSIDE

Nitroprusside is an extremely potent vascular smooth muscle relaxant that is a balanced vasodilating agent (i.e., it dilates both veins and arteries).[3,6] Its rapid onset of action and short duration of effect make it an ideal drug for treating severe left-sided heart failure in the critical care setting.[6]

179.4.1 Contraindications

- Compensatory hypertension caused by arteriovenous shunts or coarctation of the aorta
- Inadequate cerebral circulation
- During emergency surgery in critically ill patients
- Hypertrophic obstructive cardiomyopathy (nitrates can worsen the outflow obstruction)[2]
- Cardiac tamponade (because venous return to the heart is decreased, vasodilation will only lower systolic blood pressure without improving cardiac output)[2]
- Tight mitral stenosis (In this situation, left ventricular filling is decreased, lowering blood pressure will not improve stroke volume and the resultant increase in heart rate may even decrease cardiac output.[2]

179.4.2 Cautions

- Geriatric patients[8]
- Hepatic insufficiency[8]
- Renal impairment[8]
- Hyponatremia[8]
- Hypothyroidism[3]

179.4.3 Adverse Effects

Most adverse effects are related to hypotension.

- Nausea, retching, restlessness, apprehension, muscle twitching, dizziness[3] (headaches common in humans)[2]
- Syncope[2]
- Tachycardia[2]

- Irritation at the infusion site if the solution becomes extravasated[3]
- Potential thiocyanate and cyanide toxicity with continued administration[3]

179.4.4 Special Characteristics

Nitroprusside has several characteristics that require special handling. The most important is its potency as a vasodilator so that systolic blood pressure must be monitored carefully during administration. Therapy should be initiated at a dosage of 0.5 µg/kg/min and increased by 0.5 to 1 µg/kg/min every 5 minutes to a blood pressure of 90 to 100 mm Hg.[3,6] Ideally there should be continuous blood pressure monitoring with an arterial catheter, but frequent intermittent Doppler or oscillatory blood pressure measurements can also be used.[6]

Cyanide and thiocyanate toxicity are unique consequences of prolonged nitroprusside administration.[6] Cyanide is one of the by-products that is produced by the same reaction that produces NO. Free cyanide is converted to thiocyanate, either within the erythrocytes or by a transsulfuration reaction with thiosulfate by the rhodanase enzyme within the liver. Thiocyanate is freely eliminated in the kidney unless there is severe renal failure. Therefore nitroprusside should not be used in patients with severe hepatic or renal insufficiency.[6] Clinical signs of toxicity include delirium,[3] depression and stupor, seizures, and metabolic acidosis.[6] Because metabolic acidosis is an early sign of toxicity, acid-base status should be monitored frequently.[3] Because prolonged administration is one of the main causes of toxicity, it is generally recommended not to use nitroprusside for more than 48 hours.[7]

Nitroprusside is very light sensitive, so the infusion bag and intravenous line should be covered immediately after reconstitution with aluminum foil or other opaque material. Solutions that turn blue, dark red, or green should be discarded,[3] and all solutions should be discarded after 24 hours. Nitroprusside should be reconstituted only in 5% dextrose in water, and no other additives should be used.[3,6]

Interestingly, tolerance to nitroprusside does not develop because of spontaneous NO donation,[2,4] so it is not necessary to use intermittent administration.

179.4.5 Uses in Veterinary Medicine

Nitroprusside is used to treat CHF that either is refractory to treatment or is secondary to acute, severe mitral regurgitation.[3,7-10] Because of its mechanism of action it may even be more effective than furosemide in these situations.[8,10] It should not be used if the diagnosis has not been established or when blood pressure cannot be monitored.[7] Although not a common practice in veterinary medicine, nitroprusside can also be used for severe systemic hypertension.[3] Nitroprusside may be synergistic with dobutamine in catastrophic CHF.[6]

179.5 NITROGLYCERIN OINTMENT

NTG ointment is a venodilator that is commonly used in veterinary medicine for CHF.[7,9] It reduces preload, thereby reducing myocardial oxygen demand and workload.[3] Although the efficacy of transdermal nitroglycerine in CHF is uncertain, it is still routinely recommended.[7,9,10]

One of the biggest drawbacks to the use of NTG ointment is the development of tolerance.[3,9] This can be overcome by reducing the frequency of administration[9] or scheduling an 8-hour to 12-hour washout period. In addition, certain drugs (vitamin C, hydralazine, ACE inhibitors, and angiotensin receptor blockers) that are given concurrently with NTG can decrease tolerance, although they are used primarily with oral nitrates.[2,5,11]

Transdermal NTG comes in an 2% ointment that should be applied to a hairless area.[9] The dosage is empiric but usually is given at ⅛ to ¼ inch q6-8h in cats and ¼ to 2 inches in dogs.[7,3] Gloves should be worn by the person applying it[3] and the area where it is applied wiped clean before the next application.

179.6 ISOSORBIDE DINITRATE

Isosorbide dinitrate is one of the oral forms of NTG. Although it is rarely prescribed in veterinary medicine it may 769
still be useful for adjunctive therapy in dogs with CHF.[10] As with NTG ointment, tolerance can develop quickly.[12] 770
It has been combined with hydralazine in humans for effective treatment of CHF, although ACE inhibitors are still preferable.[13]

179.7 SUGGESTED FURTHER READING*

DF Hogan: In *Emergency therapy of congestive heart failure*. Conference Proceedings of the 20th Annual ACVIM Forum 2002, American College of Veterinary Internal Medicine, Dallas, TX, *A good review that discusses both diagnosis and treatment of CHF*.

LH Opie, HD White: Nitrates. In LH Opie, BJ Gersh (Eds.): *Drugs for the heart*. 6, 2005, Elsevier, Philadelphia, *An excellent human text for cardiac drugs; principles can be applied in veterinary medicine*.

D Sisson, MD Kittleson: Management of heart failure: principles of treatment, therapeutic strategies, and pharmacology. In PR Fox, D Sisson, NS Moise (Eds.): *Textbook of canine and feline cardiology*. 2, 1999, Saunders, Philadelphia, *One of the best textbooks of canine and feline cardiology*.

* See the CD-ROM for a complete list of references.

180 Chapter 180 Diuretics

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180.1 KEY POINTS

- A thorough clinical and laboratory evaluation is necessary to define clear therapeutic goals for diuretic therapy and to choose the most appropriate drug.
- The main goals for diuretic therapy are the enhanced excretion of retained water, solutes, and toxins; the promotion of urine flow; and the decrease in the urinary concentration of solutes and toxins.
- The most common indications for diuretics in the critical care patient are oligoanuric acute renal failure, decompensated chronic kidney disease, congestive heart failure, ascites from liver failure, and other fluid and electrolyte disorders.
- The use of diuretics in acute renal failure might improve the urine production and the ability to provide therapy, but it does not change directly the likelihood of renal recovery.
- The use of diuretics to treat edema is justified only for fluid retention caused by increased hydrostatic pressure. With increased vascular permeability, further depletion of the vascular volume with diuretics is rarely indicated and often is detrimental.

180.2 INTRODUCTION

Disturbances in the regulation and balance of fluid and electrolytes are very common, and they contribute significantly to the morbidity and mortality of animals treated in the critical care setting. Fluid and solute excesses are often corrected with diuretics, a heterogeneous group of drugs acting on various segments of the nephron, where they block the reabsorption of water and solutes and promote their urinary excretion. The correct assessment of electrolyte and mineral disorders is hampered by their compartmentalization, and correction of their serum concentrations is sometimes better achieved by translocation into the proper compartment.

The appropriate use of diuretics in the critical care patient requires a careful clinical and laboratory assessment and a good understanding of the underlying disease and pathophysiology in order to define clear therapeutic goals for the various fluid compartments, electrolytes, and minerals, and to choose the most appropriate diuretic, its route of administration, and dosage. Because of the complex disease processes of most critically ill animals, the limitations of their clinical assessment, and the limited data from clinical studies in small animals, this therapy remains often empiric and based on pathophysiologic justifications and clinical experience rather than on objective experimental data. The therapeutic monitoring should therefore aim to more objectively assess treatment success and anticipate or recognize side effects.

180.3 PHYSIOLOGY OF DIURESIS AND ANTIDIURESIS

One of the main characteristics of the kidney function is its ability to regulate the excretion of water and most individual solutes independently of each other.[1] In the normal animal the rate of urine excretion (diuresis) depends mostly on renal handling of water and thus on the concentration of antidiuretic hormone (ADH, vasopressin). ADH production is increased in response to elevated plasma osmolality, hypovolemia/hypotension and, to a lesser extent, as a response to nausea and increased angiotensin II concentration. ADH production is suppressed and diuresis is increased by atrial natriuretic hormone and ethanol.[1]

To exert its antidiuretic function, ADH requires a functional tubular system, a medullary concentration gradient of sodium and urea, and a functional ADH-receptor system to use this gradient. Failure of these mechanisms results in an inappropriately increased diuresis. Two additional diuretic mechanisms are involved in pathologic conditions: (1) pressure natriuresis, a negative feedback involved in hypervolemic hypertensive states leading to increased natriuresis and restoration of normovolemia and normotension, and (2) osmotic diuresis, a passive diuretic mechanism resulting from abnormal urinary concentrations of osmotically active solutes such as glucose or sodium.[1]

Therefore increased diuresis can be achieved therapeutically through exogenous loading with water or salt, administration of poorly reabsorbed solutes, and pharmacologic inhibition of the tubular reabsorption mechanisms of sodium or water. Depending on the mechanisms involved, the diuretic effect will be associated with extracellular fluid (ECF) volume expansion (hypervolemic diuresis) or depletion (hypovolemic diuresis).

180.4 PHARMACOLOGY

Diuresis can be induced osmotically or, more commonly, by pharmacologic blockade of sodium reabsorption at various sites along the nephron. The basic rule is that, although they can modulate a greater bulk of sodium, efficacy of proximal diuretics may be overcome by distal compensatory increases in sodium reabsorption in the loop of Henle. The efficacy of distal diuretics on the other side is limited by the small portion of sodium actually reaching the distal tubule. Diuretics acting at the loop of Henle are thus most effective because of the large amount of filtrate delivered to this site and the lack of an efficient reabsorptive region beyond their site of action.[2]

Diuretics are grouped according to their mechanism of action and they include, in order of their renal tubular target, osmotic diuretics, carbonic anhydrase (CA) inhibitors, loop diuretics, thiazide diuretics, aldosterone antagonists, and other potassium-sparing distal diuretics (Table 180-1). Mannitol and furosemide are used most frequently in the critical care setting; consequently the other diuretics will be mentioned here only briefly. Usual dosage recommendations are summarized in Table 180-2. In using diuretics it is important to note that fluid therapy should be adjusted closely to the desired goals of the global therapy. For example, if the therapeutic goal is a depletion of the ECF with furosemide in an animal with CHF, it does not make sense to administer intravenous fluids concomitantly. Partial free water replacement with 5% dextrose in water may be an exception in this scenario.

All diuretics except spironolactone reach their tubular sites of action through the urinary space. Mannitol is freely filtered in the glomeruli, and the other highly protein-bound diuretics are secreted actively through the organic acid and organic base pathways into the proximal tubule.[2] This explains the decreased efficacy of most diuretics in animals with renal disease. However, the impaired tubular secretion and delivery to the site of action can be compensated partially by a progressive titration to higher plasma concentrations. In animals with proteinuria and nephrotic syndrome, the serum diuretic concentration remains low as a result of hypoproteinemia and results in decreased tubular secretion of the diuretic that is then partially neutralized by binding to urinary proteins. Dose and frequency adjustments can partially compensate for this and provide sufficient concentrations of the active drugs at the site of action.[2,3] Serial measurements of urinary electrolytes can provide a more objective assessment of diuretic efficacy to help guide therapeutic decision making, such as dosage adjustments and combining diuretics from different classes.

Tolerance and inefficacy of diuretic therapy can happen after a single dose as a result of depletion of the ECF. In the long term, hypertrophy of the distal nephron reflects an increased compensatory solute reabsorption of the distal sites to compensate for proximal tubular blockade. This hypertrophy parallels a progressive loss of drug efficacy and the requirement for higher doses or a sequential blockade of multiple sodium reabsorption sites.[2-4]

180.4.1 Osmotic Diuretics

Mannitol is an osmotically active, nonreabsorbed sugar alcohol that is administered intravenously for its osmotic or diuretic properties, or both. The resulting hyperosmolality of the ECF creates a water shift from the intracellular fluid (ICF) compartment and an initial expansion of the ECF. The contraction of the ICF is used therapeutically in animals with cerebral edema associated with increased ICF and increased intracranial pressure (trauma, fluid shifts secondary to a rapid correction of hyperglycemia, hypernatremia, or azotemia).[5-7] Mannitol is freely filtered by the glomerulus (molecular weight 182 Da) and does not undergo tubular reabsorption, resulting in increased tubular flow rate and osmotic diuresis. The increased urine flow reduces the tubular reabsorption of urea, increasing its urinary clearance and thus decreasing its serum concentration.[1,4] This property can be used to intensify fluid diuresis and to accelerate recovery of clinical and metabolic stability in animals with decompensated chronic renal disease, even in nonoliguric states.

Additional potential benefits of mannitol for acute renal injury include decreased renal vascular resistance, decreased hypoxic cellular swelling, decreased renal vascular congestion, decreased tendency of erythrocytes to aggregate, protection of mitochondrial function, decreased free radical damage, and even renoprotection when administered before a toxic or ischemic insult.[1,4,8] There are, however, no data to support a clinical benefit in animals with established renal failure, and its use is based purely on extrapolations and pathophysiologic justifications. Very high doses of mannitol have been described as causing acute tubular injury in humans, and its use should thus remain cautious in oliguric animals to avoid accumulation, volume overload, hyperosmolality, and further renal damage.[1,9]

180.4.2 Carbonic Anhydrase Inhibitors

Acetazolamide inhibits mostly the type II (cytoplasmic) and IV (membrane) CAs from the proximal tubular epithelium, resulting in a net decrease in the proximal reabsorption of sodium bicarbonate. The resulting metabolic acidosis and natriuresis are self-limiting, because progressively less bicarbonate is filtered and the proximal tubular epithelium becomes less responsive to CA inhibition. Furthermore, the proximal site of action of CA inhibitors leads to a compensatory increase in the distal sodium absorption.

CAs are also located in other organs and their inhibition is variable: blockade of ocular and brain CA decreases the production of aqueous humor and CSF, respectively; blockade of red blood cell CA hampers carbon dioxide removal from the tissues; the gastric CA is affected only minimally by inhibitors. CA inhibitors rarely are used as diuretics except in some combination protocols, and their main clinical application is for the treatment of elevated intraocular pressure in glaucoma.[1,2,4]

Table 180-1 Site of Action and Effect of the Most Common Diuretics

			Global Effect on			
Class	**Prototype Drug**	**Site of Action**	**Water**	**Electrolytes**	**Minerals**	**Acid-Base**
Osmotic diuretics	Mannitol	All segments (mostly LH)	↓ TBW ↓ ICF ↑ ECF	↓ Na, K, Cl	↓ Ca, P, Mg	—
CA inhibitors	Acetazolamide	PT (+ late DT)	↓ TBW	↓ Na, K, Cl	↓ P	Metabolic acidosis
Loop diuretics	Furosemide	TAL	↓ TBW	↓ Na, K, Cl	↓ Ca, P, Mg	Metabolic alkalosis
Thiazide diuretics	Hydrochlorothiazide	Early DT	↓ TBW	↓ Na, K, Cl	↓ P, Mg ↑ Ca	—
Aldosterone antagonists	Spironolactone	Late DT, CD	↓ TBW	↓ Na, Cl ↑ K	↓ Ca	Metabolic acidosis
Distal diuretics	Amiloride, triamterene	Late DT, CD	↓ TBW	↓ Na, Cl ↑ K	±↑ Ca	—

Ca, Calcium; *CA,* carbonic anhydrase; *CD,* collecting duct; *Cl,* chloride; *DT,* distal tubule; *ECF,* extracellular fluid volume; *ICF,* intracellular fluid volume; *K,* potassium; *LH,* loop of Henle; *Mg,* magnesium; *Na,* sodium; *P,* phosphorus; *PT,* proximal tubule; *TAL,* thick ascending limb of the loop of Henle; *TBW,* total body water; ↓/↑, decreased/increased balance.

Table 180-2 Dosages of Most Commonly Used Diuretics

Drug	Indication	Dosage
Mannitol	Renal failure	0.25 to 1 g/kg IV q4-6h CRI 1 to 2 mg/kg/min when diuresis instituted
	Glaucoma	1 to 3 g/kg IV once
	Cerebral edema	1 to 1.5 g/kg IV once
Acetazolamide	Glaucoma	50 mg IV once, then 2 to 10 mg/kg q8-12h PO 7 mg/kg PO q8h in the cat
Furosemide	Diuretic	0.5 to 4 (max 8) mg/kg IV, IM, SC, PO q8-12h CRI 2 to 15 µg/kg/min
Hydrochlorothiazide	Diuretic	0.5 to 5 mg/kg PO q12-24h
Spironolactone	K-sparing diuretic	1 to 4 mg/kg PO q12-24h
Amiloride	K-sparing diuretic	0.1 to 0.3 mg/kg PO q24h
Triamterene	K-sparing diuretic	1 to 2 mg/kg PO q12h

CRI, Constant rate infusion; *IM,* intramuscular; *IV,* intravenous; *K,* potassium; *PO,* per os; *SC,* subcutaneous.

180.4.2.1 Loop Diuretics

The prototype loop diuretic furosemide binds to and inhibits the Na-K-2Cl cotransporter on the apical membrane of epithelial cells of the thick ascending limb of the loop of Henle. The decreased sodium and chloride reabsorption results in marked natriuresis and diuresis, and will rapidly dissipate the medullary osmotic gradient.[10] Increased distal delivery of sodium leads to a sodium-potassium exchange and promotes kaliuresis. The blockade of the secondary active Na-K-2Cl cotransporter decreases the energy expenditure and the oxygen consumption of the tubular epithelial cells and can be beneficial in ischemic conditions. Furosemide improves further the renal parenchymal oxygen supply by decreasing renal vascular resistance and increasing renal blood flow. Blockade of the chloride flux in the macula densa inhibits the important regulatory tubuloglomerular feedback, and the kidney may not be able to adjust its glomerular filtration in response to tubular loss of solutes.[1-4]

The potential concerns and benefits of furosemide in renal disease are based mostly on pathophysiologic justifications and not on controlled clinical studies. The combination of mannitol with furosemide seems to be synergistic in inducing diuresis in dogs with acute renal failure. The use of furosemide for ECF contraction in small animals with CHF is better described. The decreasing responsiveness to loop diuretics in heart failure is mostly a result of the compensatory increase in reabsorption of sodium in the distal tubule, and it commonly requires a combination with a more distal diuretic for sequential nephron blockade. The relatively long dosage interval for furosemide compared with its elimination half-life (1 to 1.5 hours in dogs) can result in intermittent rebound sodium retention and diminish its efficacy. Frequent administration or constant rate infusion are required when maximal efficacy is desired.[3,11]

180.4.2.2 Thiazide Diuretics

Thiazide diuretics exert their action by inhibiting the Na-Cl cotransporter on the apical membrane of the distal tubule. They have only a few indications in small animal medicine, in which they are used mostly for their 771
anticalciuretic properties in the long-term prevention of calcium-containing uroliths or with other diuretics in 773
combination protocols.[2,12] Thiazides paradoxically reduce urine production in severely polyuric animals with diabetes insipidus, by inducing a mild hypovolemia and increasing proximal tubular sodium conservation.[1,13]

180.4.2.3 Aldosterone Antagonists

Spironolactone and eplerenone competitively antagonize aldosterone by binding to its receptor on the late distal tubule and the collecting duct to increase sodium, calcium, and water excretion and decrease potassium loss. Spironolactone is most efficacious in hyperaldosteronism and this defines its main clinical applications in liver and heart failure, usually associated with a more efficient loop diuretic.[1,2,4] Spironolactone also seems to have a positive effect on myocardial remodeling and reduction of cardiac fibrosis.[14] It is commonly combined with other diuretics to reduce their potassium-wasting effects.

180.4.2.4 Other Potassium-Sparing Distal Diuretics

Amiloride and triamterene inhibit the electrogenic sodium reabsorption in the late distal tubule and the collecting duct, suppressing the driving force for potassium secretion. Their distal site of action gives them only weak diuretic and natriuretic properties, and they are used mostly to enhance the efficacy and counterbalance the potassium-wasting effect of proximal diuretics.[2,4]

180.4.3 INDICATIONS FOR DIURETIC THERAPY

Diuretics are used commonly in the critical care setting, mostly for urinary and cardiac diseases. A partial list of further indications is provided in Table 180-3.

180.4.3.1 Urinary Diseases

The use of diuretics to convert the oligoanuria of acute renal failure to a nonoliguric state is controversial. Although successful initiation of diuresis can facilitate or even just allow the conventional therapy of previously anuric animals, it has no prognostic value and it does not imply further improvements in renal function. Urine production, although necessary, does not equate with renal recovery.

High dosages of furosemide are often combined with mannitol after initial rehydration of the oligoanuric animal. The addition of a so-called *renal dosage* of dopamine (0.5 to 3 μg/kg/min) is no longer recommended because of a lack of demonstrable survival benefit and the potential for side effects such as vasoconstriction and hypertension.[15] When dialytic therapy is available, these diuretic maneuvers are neither indicated nor necessary, because the electrolyte and fluid disturbances can be corrected directly by dialysis.

The oliguria of chronic renal disease is rarely an indication for diuresis in animals, because most patients in this terminal stage are no longer manageable conventionally. Fluid overload is a feature of end-stage disease and would be treated with dialytic fluid removal and restriction of water intake. The efficacy of diuretics is markedly decreased at this stage because of their poor delivery at the tubular site of action (see previous discussion). However, mannitol is used in animals with decompensated chronic renal disease to intensify the diuretic support (fluid therapy) and temporarily improve the azotemia by decreasing the tubular reabsorption of urea and increasing its urinary clearance. This strategy can accelerate the clinical and metabolic recovery of these animals.

Table 180-3 Indications and Goals for Diuretic Therapy

Indication	Main Goal(s)	Diuretic Strategy
Oligoanuria (ARF)	Restore diuresis ↓ Tubular obstruction ↑ Kaliuresis	Furosemide, mannitol (after rehydration)
Uremic crisis (CKD)	↓ BUN	Mannitol (after rehydration) + fluid therapy
Nephrotic syndrome	↓ Interstitial fluid volume	Furosemide
Urinary diseases (urolithiasis, cystitis)	↑ Urine flow	Water, ± salt, thiazides
Congestive heart failure	↓ Preload, ↓ ECF ↓ Pulmonary edema or pleural effusion	Furosemide, ± combination with spironolactone
Hypertension	↓ Preload and IVV	Thiazides, furosemide
Liver failure	↓ Interstitial fluid volume	Spironolactone, ± furosemide
Hypercalcemia	↑ Calciuresis	Furosemide + NaCl 0.9%
Hyperkalemia	↑ Kaliuresis	NaCl 0.9%, furosemide
Iatrogenic fluid overload	↓ TBW	Furosemide
↑ Intracranial pressure	↓ ICF	Mannitol
Glaucoma	↓ IOP	Acetazolamide, (mannitol)
Diabetes insipidus	↓ Polyuria	Thiazides

ARF, Acute renal failure; *BUN,* blood urea nitrogen; *CKD,* chronic kidney disease; *ECF,* extracellular fluid volume; *ICF,* intracellular fluid volume; *IOP,* intraocular pressure; *IVV,* intravascular volume; *NaCl,* sodium chloride; *TBW,* total body water; *UOP,* urine output; ↓/↑, decreased/increased balance.

Treatment of the edematous state of the nephrotic syndrome is oriented toward decreasing the proteinuria and improving the hypoalbuminemia, to correct the disturbances of this overhydrated but hypovolemic condition. However, when the clinical response is delayed or insufficient, diuretics such as furosemide may be necessary to symptomatically reduce edema and effusions and to improve the quality of life. They need to be titrated to the minimal clinically effective dosage to overcome the decreased efficacy in this disease (see previous discussion) and to avoid further depletion of the vascular volume and renal decompensation.[2-4]

Diuretics are sometimes indicated in lower urinary tract diseases of dogs and cats to decrease the concentration of inflammatory mediators (idiopathic feline lower urinary tract disease in cats) or of calculogenic minerals (urolithiasis). This is typically a long-term therapy achieved mostly by hypervolemic diuresis using increased water or salt intake, along with dietary modifications. Thiazide diuretics selectively decrease calciuresis and can be indicated in animals with recurrent calcium oxalate urolithiasis.[12] 773

180.4.3.2 Congestive Heart Failure

CHF usually is treated with loop diuretics, if possible, in combination with dietary sodium restriction, despite the potential for activation of the renin-angiotensin-aldosterone system.[16] The progressive tolerance to loop diuretics can be balanced by a combination with distal diuretics, mostly thiazides, although spironolactone is used increasingly for its beneficial effect on myocardial remodeling.[2,14] Serum potassium concentration should be monitored carefully when using potassium-wasting diuretics in the patient with cardiac disease, because hypokalemia enhances the risk of digoxin toxicity.[2]

180.4.3.3 Liver Failure

Animals with end-stage liver failure commonly develop ascites and edema as a result of hypoalbuminemia, activation of the renin-angiotensin-aldosterone system, and portal hypertension.[2] Symptomatic relief of the resulting abdominal distention can be obtained by abdominocentesis, but rapid refill of the abdominal cavity can result in hypovolemia and shock. The aldosterone antagonist spironolactone is the first-choice diuretic for this disease process, and it is often combined with loop diuretics for a sustained and progressive reduction of ascites. Because this diuretic effect happens at the expense of an already depleted intravascular volume, the diuretics should be titrated to the minimally effective dosage necessary to obtain acceptable symptomatic relief of discomfort, similarly to animals with protein-losing nephropathy and enteropathy.[2]

180.4.3.4 Electrolyte and Mineral Disorders

Fluid therapy and loop diuretics can help correct temporarily the hyperkalemia in an animal with a functional urinary system until the underlying cause can be identified and corrected.[2] Similarly, severe hypercalcemia can be reduced and renal function preserved with high dosages of furosemide and matching rates of physiologic saline infusion until a diagnosis is obtained and a causal therapy is instituted. The efficacy of this treatment in severe hypercalcemia is often insufficient and requires additional calcium-reducing therapies.[2,4]

180.4.3.5 Systemic Hypertension

Treatment of systemic hypertension in small animals is based mostly on the use of vasodilators, which can activate the renin-angiotensin-aldosterone system over the long term, leading to salt and water retention. Because spontaneous and iatrogenic expansion of the ECF are frequent in hypertensive animals with renal disease, refractory cases commonly require combinations of vasodilators, negative chronotropic drugs, and loop or thiazide diuretics.[2]

180.4.4 SUGGESTED FURTHER READING*

DM Boothe: Drugs affecting the kidneys and urination. In DM Boothe (Ed.): *Small animal clinical pharmacology and therapeutics*. 2001, Saunders, Philadelphia, *Concise but very thorough description of the clinical pharmacology of diuretics in animals. The most practical review of diuretics and their veterinary applications*.

DC Brater: Diuretic therapy. *N Engl J Med*. **339**, 1998, 387, *Excellent human medicine review in the tradition of the* New England Journal of Medicine *with a good mix of in-depth discussions and direct practical applications. Addresses many issues directly applicable to the veterinary patient*.

JM McClellan, RE Goldstein, HN Erb, et al.: Effects of administration of fluids and diuretics on glomerular filtration rate, renal blood flow, and urine output in healthy awake cats. *Am J Vet Res*. **67**, 2006, 715, *An experimental study documenting the hemodynamic and functional effects of diuretics (saline infusion, mannitol, furosemide-dopamine) in the cat*.

BD Rose, TW Post: In *Clinical physiology of acid-base and electrolyte disorders*. ed 5, 2001, McGraw-Hill, New York, *Very detailed description of the physiology of diuresis and the mode of action of diuretics, including some clinical correlates. The best reference book for a deeper understanding of the physiology of fluid and electrolyte disorders*.

CS Wilcox: Diuretics. In BM Brenner (Ed.): *Brenner & Rector's the kidney*. 2004, Saunders, Philadelphia, *Most detailed review including all aspects from the molecular biology to the clinical application of diuretics. The “bible” of human nephrology*.

* See the CD-ROM for a complete list of references

181 Chapter 181 Gastrointestinal Protectants

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181.1 KEY POINTS

- Histamine-2 receptor antagonists (H_2RAs) are competitive inhibitors of gastric acid secretion, meaning that they lower gastric acid secretion but do not abolish it. However, they also diminish pepsin secretion.
- Ranitidine and nizatidine are H_2RAs that are also gastric prokinetic agents.
- Cimetidine inhibits hepatic P-450 cytochrome enzyme activity so much that it can be used therapeutically (e.g., to minimize acetaminophen toxicity) or can delay metabolism of drugs.
- Proton pump inhibitors (PPIs) are noncompetitive inhibitors of gastric acid secretion, meaning that they can inhibit gastric acid secretion to a greater extent than H_2RAs. However, it can take 2 to 5 days for them to achieve maximal effectiveness when given orally.
- Sucralfate is an unabsorbed drug that binds to ulcerated or eroded mucosa. It can adsorb other drugs, delaying or inhibiting their absorption.
- Misoprostol is a prostaglandin analog that was designed to prevent ulceration and erosion due to nonsteroidal antiinflammatory drugs (NSAIDs). However, it is not as effective or reliable in preventing NSAID-induced ulceration in dogs as it is in humans.
- Orally administered antacids that are used to neutralize gastric acid have a shorter duration of action and rarely are used to manage or prevent ulcers and erosions in veterinary medicine.

181.2 INTRODUCTION

Gastrointestinal ulceration and erosion (GUE) is an important problem in dogs, but much less common in cats. Stress (defined here as anything causing substantial hypoperfusion or anoxia of the gastric mucosa) and drug therapy (especially nonsteroidal antiinflammatory drugs [NSAIDs] but also dexamethasone) are especially common causes of GUE in dogs. Prednisolone at dosages commonly administered is rarely ulcerogenic unless there is concurrent gastric hypoxia or hypoperfusion, severe spinal disease, or concurrent use of NSAIDs. Stress ulceration may be due to hypotensive shock, systemic inflammatory response syndrome, severe life-threatening illness, and extreme exertion. Hyperacidity (usually caused by gastrinoma or mast cell tumor) may cause GUE, but more commonly causes duodenal as opposed to gastric lesions. Hepatic failure, renal failure tumors, and, to a much lesser extent, foreign bodies may also cause GUE.

Gastrointestinal (GI) protectants are primarily indicated to heal existing gastric ulcers and erosions. Removing the cause of the ulceration or erosion markedly enhances efficacy, as does maintaining GI perfusion. Protectants are often poorly effective at preventing ulceration when the cause (e.g., use of NSAIDs, continued poor perfusion or anoxia to the gastric mucosa) persists. However, when there is a known cause of ulceration or erosion that cannot be readily alleviated, these drugs are often given in the hope that they will at least retard, if not prevent, ulceration. See Table 181-1 for a list of commonly used GI protectants and dosages.

Proton pump inhibitors (PPIs) and H_2RAs prevent ulceration caused by certain forms of stress (i.e., probably a combination of poor gastric mucosal blood flow, hypoxia, and possibly other factors) in dogs.[1] None of the drugs discussed in this chapter has shown clear efficacy in preventing ulceration due to steroids (e.g., dexamethasone, methylprednisolone sodium succinate),[2–4] and although helpful against NSAIDs-induced GUE, they typically are not completely effective.[5–9] There is no evidence that combination therapy (e.g., using H_2RAs plus sucralfate) is any more effective than using just one drug.

Drugs decreasing gastric acid secretion or otherwise used for managing gastric ulceration and erosion are not antiemetics in the strict sense (i.e., they have no effect on the medullary vomiting center or the chemoreceptor trigger zone); however, they can have an antidyspeptic effect that lessens nausea. Therefore they may be used to stimulate appetite or to enhance the efficacy of true antiemetics. When used to manage existing ulcers or erosions, one generally expects to see some evidence of improvement (i.e., less nausea, less bleeding) within 2 to 5 days of beginning therapy, assuming that the initiating cause has been eliminated. If there is no evidence of improvement in that time, endoscopic evalaution and/or surgical removal should be considered.

181.3 HISTAMINE-2 RECEPTOR ANTAGONISTS

The most commonly used H_2RAs in dogs and cats are cimetidine, ranitidine, and famotidine; nizatidine has not become as popular in veterinary medicine despite its good efficacy in humans. The H_2RAs work by blocking the histamine receptor on the gastric parietal cell.[10–12] They are competitive inhibitors of gastric acid secretion, meaning that they will not decrease gastric acid secretion as well as the noncompetitive PPIs. However, they have their maximal effect on decreasing gastric acid secretion almost immediately. Nizatidine and ranitidine also have reasonable gastric prokinetic activity, probably via antiacetylcholinesterase activity.

Cimetidine and ranitidine are the least potent and famotidine the most potent H_2RA, with nizatidine being intermediate. Recent work suggests that ranitidine might not be as effective an antacid in dogs as previously thought, however, further work is needed to confirm or deny this. Famotidine has the longest duration of action. With oral administration, cimetidine absorption is delayed by food, but absorption of ranitidine, nizatidine, and famotidine is not. Famotidine, ranitidine, and cimetidine undergo substantial first-pass metabolism in the liver, but nizatidine does not. Nizatidine is the most bioavailable and famotidine the least when administered orally. Cimetidine and ranitidine are metabolized extensively by the liver, but famotidine and nizatidine are excreted almost completely unchanged in the urine. It has been suggested that the dosage of cimetidine and famotidine be reduced in patients with renal failure; however, it is not known how important such a dosage reduction is.

Table 181-1 Selected Gastric Protectants That Are Used in Dogs and Cats

Drug	Mechanism of Action	Dosage	Special Considerations
Cimetidine	H_2-receptor antagonist	5 to 10 mg/kg IV, IM, SC, PO q6-8h	Potent inhibitor of hepatic P-450 enzymes Can affect metabolism of toxins or other drugs Decreases hepatic blood flow Food delays absorption
Ranitidine	H_2-receptor antagonist	*Dogs:* 0.5 to 2 mg/kg IV or 1 to 4 mg/kg PO q8-12h *Cats:* 2.5 mg/kg IV or 3.5 mg/kg PO q8-12h daily	Has prokinetic activity Has minimal effect on hepatic enzyme function
Famotidine	H_2-receptor antagonist	0.5 to 1 mg/kg IV, IM, SC, PO q12-24h	Longest acting and most potent H_2-receptor antagonist
Nizatidine	H_2-receptor antagonist	*Dogs:* 2.5 to 5 mg/kg PO q24h daily	Exclusively eliminated by kidneys
Omeprazole	Proton pump inhibitor	0.7 to 1 mg/kg PO q24h	Inhibits hepatic P-450 enzymes May cause elevations in liver enzymes Sometimes causes diarrhea
Esomeprazole	Proton pump inhibitor	0.5 to 1 mg/kg IV q24h*	
Lansoprazole	Proton pump inhibitor	1 mg/kg given IV q24h	Anecdotal
Pantoprazole	Proton pump inhibitor	1 mg/kg given IV q24h daily	Anecdotal
Misoprostol	Prostaglandin analog	2 to 5 µg/kg PO q6-12h	Can cause abortion Often causes transient diarrhea
Sucralfate	Local-acting barrier	*Dogs:* 0.5 to 1 g PO q6-12h daily *Cats:* 0.25 g PO q6-12h	Adsorbs many other drugs, slowing their absorption

H_2, Histamine-2; *IM,* intramuscular; *IV,* intravenous; *PO,* per os; *SC,* subcutaneous.

Cimetidine markedly inhibits hepatic P-450 enzymes. This effect is important and has been used therapeutically to lessen the severity of acetaminophen intoxication. However, cimetidine also decreases metabolism of theophylline, lidocaine, metronidazole, and many other drugs, resulting in higher blood levels and even toxicity in some cases. Ranitidine has less effect on these enzymes, and famotidine and nizatidine have almost no such effect. Cimetidine also decreases hepatic blood flow by about 20% and will adsorb some other drugs, delaying their absorption.

Side effects are uncommon with H_2RAs, with cimetidine tending to have more than ranitidine or famotidine. Central nervous system aberrations and cytopenias are reported in humans and are anecdotally reported in dogs. There are anecdotal reports of famotidine causing hemolytic anemia in uremic cats.

* Extrapolated dosage.

181.4 PROTON PUMP INHIBITORS

Omeprazole is the PPI that has been most commonly used in veterinary medicine. There is very limited experience with lansoprazole, pantoprazole, and esomeprazole in veterinary medicine. In people, lansoprazole has greater bioavailability than omeprazole, which might be advantageous. Both lansoprazole, esomeprazole, and pantoprazole can be given intravenously, which is advantageous in vomiting patients.

The PPI drugs irreversibly inhibit hydrogen-potassium ATPase on the luminal side of the parietal cell, thus stopping secretion of hydrogen ions into the gastric lumen.[11-12] However, omeprazole is susceptible to destruction by gastric acid, so it is administered as enteric-coated granules that are absorbed in the duodenum. Absorption is diminished by food; therefore this drug should be given on an empty stomach. Once absorbed, omeprazole undergoes first-pass metabolism by the liver, and the rest is selectively sequestered in the acidic environment of the parietal cells where it is transformed to the active drug. Therefore it is best to administer the drug about 1 hour before feeding the patient so as to maximize the acidity of the parietal cell, thereby increasing the amount of omeprazole sequestered there.

This complex pharmacologic pathway means that it usually takes 2 to 5 days before the maximal effect of omeprazole occurs. However, once omeprazole has been used for 3 to 5 days, it can generally produce a greater degree of acid suppression than the H_2RAs.[13] Furthermore, suppression of gastric acid secretion will continue for a few days after ceasing administration of the PPI because of the irreversible nature of inhibition of the proton pump enzyme.

Despite the greater efficacy of omeprazole, it seems infrequent that a PPI is actually required in a dog or a cat with 776

777 gastric or duodenal ulceration because H_2RA therapy failed, with the exception of severe esophagitis and duodenal ulceration due to paraneoplastic hyperacidity (e.g., mast cell tumors or gastrinomas). Therefore it is usually appropriate to administer an H_2RA to a patient with GUE first and use a PPI only if the first therapy fails. There are relatively few side effects associated with PPIs, with diarrhea being reported in humans and dogs. Omeprazole does inhibit the hepatic P-450 enzymes and may cause elevations in liver enzymes. The markedly increased gastric pH can affect absorption of some drugs such as ketoconazole and digoxin.

181.5 SUCRALFATE

Sucralfate is the octasulfate of sucrose combined with aluminum hydroxide. This is a locally acting drug that is only given orally, either as a tablet or as a suspension. In the acidic environment of the stomach, it becomes viscous and binds tightly to epithelial cells, and especially to the base of erosions and ulcers where it may remain for 6 hours. While adhered to the ulcer or erosion, it serves as a physical barrier, protecting the ulcer from pepsin and bile acids, as well as stimulating local production of prostaglandins and binding to epidermal growth factor (which favors mucosal repair). It has almost no adverse side effects besides sometimes causing constipation (which can be used therapeutically in some patients with diarrhea). Sucralfate can adsorb other drugs (e.g., enrofloxacin), which slows their systemic absorption. It should be given before antacid therapy to maximize efficacy and should not be given with enteral feedings because it may bind the fat-soluble vitamins. A major disadvantage is that sucralfate can only be given orally, which limits its usefulness in vomiting patients.

181.6 PROSTAGLANDIN ANALOGS

Misoprostol is a prostaglandin E_1 analog that has both antacid and mucosal protective properties (i.e., it stimulates secretion of mucus and bicarbonate, plus it increases gastric mucosal blood flow). The antisecretory effect on the gastric acid is probably the more important. It acts directly on parietal cells to inhibit both nocturnal acid secretion as well as secretions in response to food, pentagastrin, and histamine. The drug is absorbed rapidly and undergoes first-pass metabolism in the liver to the active form. Food delays absorption. Misoprostol has a short half-life and must be given 2 to 3 times daily.

This drug was developed specifically as an agent to prevent ulceration caused by prostaglandin inhibition from NSAIDs.[11,12] In veterinary medicine its greater cost, need for frequent administration, and high rate of side effects usually mean that it is given only to patients that fail other medical therapies or have difficulty tolerating NSAIDs that they must receive in order to maintain a good quality of life. It is not as clearly effective in protecting dogs receiving NSAIDs as it has been reported to be in humans. Side effects include diarrhea and uterine contraction (which can result in abortion in pregnant females). Diarrhea often subsides after 2 to 5 days.

181.7 ANTACIDS

Numerous drugs are administered orally for neutralizing gastric acid. These drugs are usually not used for treating or preventing gastric ulcers because they tend to have a relatively short half-life compared with H_2RAs and PPIs. Furthermore, each set of drugs tends to have its own idiosyncrasies. Aluminum and magnesium compounds are known for their ability to delay or prevent absorption of other drugs.

181.8 SUGGESTED FURTHER READING*

DM Boothe: Gastrointestinal pharmacology. In DM Boothe (Ed.): *Small animal clinical pharmacology and therapeutics*. 2001, Saunders, Philadelphia, *A veterinary text that describes the use of these drugs in dogs and cats.*

WA Hoogerwert, PJ Pasricha: Agents used for control of gastric acidity, treatment of peptic ulcers and gastroesophageal reflux disease. In JG Hardman, LE Limbird (Eds.): *Goodman's and Gilman's the pharmacological basis of therapeutics*. ed 10, 2001, McGraw-Hill, New York, *A detailed discussion of the mechanisms of gastric acid secretion and the pharmacologic properties of the various drugs.*

KR McQuaid: Drugs used in the treatment of gastrointestinal diseases. In BG Katzung (Ed.): *Basic and clinical pharmacology*. ed 9, 2004, Lange Medical Books/McGraw-Hill, New York, *A detailed discussion of the pharmacologic properties of the various drugs.*

* See the CD-ROM for a complete list of references

182 Chapter 182 Antiemetics

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182.1 KEY POINTS

- Centrally acting antiemetics are generally much more effective than peripheral-acting antiemetics. Centrally acting antiemetics that work on the medullary vomiting center are often more effective than those that act just at the chemoreceptor trigger zone.
- Promazine derivatives (e.g., chlorpromazine, prochlorperazine) are effective centrally acting antiemetics, but they can cause hypotension due to α-adrenergic blocking activity.
- Metoclopramide works at the chemoreceptor trigger zone and is also a gastric prokinetic. Metoclopramide can sometimes cause abnormal behavior and even vomiting (possibly due to excessive gastric prokinetic activity).
- The 5-HT_3 receptor antagonists ondansetron and dolasetron are among the most effective antiemetics used in dogs and cats, and they have very few side effects.
- Maropitant is a newly approved centrally acting antiemetic for use in dogs, but clinical experience with this drug is limited.

182.2 INTRODUCTION

Antiemetics are indicated primarily in patients that are vomiting so much that it is difficult to maintain fluid or electrolyte homeostasis, or patients with severe nausea that is obviously diminishing their quality of life (Table 182-1). Depending on individual particulars, it is sometimes appropriate to allow a patient to vomit once or twice a day in order to see if other therapy is having a beneficial effect on the underlying cause. Typical indications include pancreatitis, gastritis or enteritis, peritonitis, hepatic disease, renal insufficiency, and patients that are recumbent or at high risk for aspiration pneumonia. These drugs are usually ineffective in patients with gastrointestinal (GI) obstruction. Parenteral administration is preferred because oral administration may be ineffective if the drug is vomited before it is absorbed.

Table 182-1 Centrally Acting Antiemetics Commonly Used in Dogs and Cats

Drug	Dosage	Special Considerations
Chlorpromazine	0.5 mg/kg IM, SC q8-12h	Can cause hypotension and sedation
Prochlorperazine	0.1 to 0.5 mg/kg IM, SC q8-12h	—
Metoclopramide	0.1 to 0.5 mg/kg IV, IM, PO q8-12h or CRI of 1 to 2 mg/kg IV q24h	Potent gastric prokinetic Can cause extrapyramidal effects if overdosed
Ondansetron	0.5 to 1 mg/kg IV, PO q12-24h	—
Granisetron	1 mg/kg IM q8-24h	—
Dolasetron	0.6 to 1 mg/kg IV, SC, PO q24h	—
Maropitant	1 mg/kg SC, q24h or 2 mg/kg PO q24h	Newly approved drug for dogs

CRI, Constant rate infusion; *IM,* intramuscular; *IV,* intravenous; *PO,* per os; *SC,* subcutaneous.

182.3 PROMAZINE DERIVATIVES

Promazine derivatives are considered broad-spectrum, centrally acting antiemetics,[1-3] being effective against most causes of nausea except inner ear problems; plus, they are inexpensive. They have antidopaminergic and antihistaminic effects that block the chemoreceptor trigger zone, and at higher dosages they block the medullary vomiting center. These drugs also have anticholinergic, antispasmodic, and α-adrenergic blocking effects. The promazine derivatives used most commonly as antiemetics in small animal veterinary medicine are chlorpromazine, prochlorperazine,[4] and acepromazine. Chlorpromazine typically is used at 0.1 to 0.5 mg/kg IV, SC, or IM q6-8h, and prochlorperazine is used at 0.1 to 0.5 mg/kg IV or SC q8-12h. The antiemetic effect of these drugs is typically evident at dosages far below those causing sedation; however, varying degrees of vasodilation may occur, producing hypotension. Therefore caution is necessary with the use of these drugs in dehydrated or hypotensive patients, and intravenous fluid therapy may be necessary.

Promazine drugs have been reported to cause increases in central venous pressure and changes in heart rate (bradycardia or tachycardia), and they possess antiarrhythmic qualities in the dog. These drugs were previously reported to lower the seizure threshold, but this has recently been called into doubt.[5] The promazines are metabolized by the liver and can cause central nervous system (CNS) signs in patients with substantial hepatic insufficiency, especially in patients with congenital portosystemic shunts. It has been suggested that prochlorperazine, and perhaps other promazine derivatives, not be used concurrently with metoclopramide because these drugs may potentiate extrapyramidal effects.[4]

182.4 METOCLOPRAMIDE

Metoclopramide is a popular antiemetic in small animal medicine. Its antidopaminergic activity and ability to block 5-HT_3 receptors result in it being a potent blocker of the chemoreceptor trigger zone. Typically given at 0.1 to 0.5 mg/kg IV, SC, or PO, metoclopramide also has potent gastric prokinetic activity that facilitates stomach emptying. This combination of mechanisms should be very effective; however, clinical practice has shown that metoclopramide is often inadequate in patients with a strong stimulus to vomit (e.g., pancreatitis, renal failure). Its efficacy can be enhanced if it is administered as a constant rate infusion (1 to 2 mg/kg q24h). The drug is sensitive to light, so the IV solution should be covered to prevent loss of efficacy. Humans undergoing chemotherapy, metoclopramide's efficacy seems to be enhanced by concurrent administration of low-dose dexamethasone, but this has not been tested critically in dogs or cats.

Metoclopramide is excreted by the kidneys, and care must be taken when using it in patients with substantially decreased glomerular filtration. If high blood levels occur as a result of renal dysfunction or overdosage, extrapyramidal signs (i.e., behavioral changes, apparent hallucinations) may occur. Such patients may appear to be affected with an overdose of an amphetamine.

182.5 5-HT$_3$ RECEPTOR ANTAGONISTS

Ondansetron, granisetron,[6] and dolasetron[7] are antiemetics that were developed in an effort to provide relief to humans severely nauseated by chemotherapy. These drugs are competitive blockers of 5-HT$_3$ receptors, and these receptors are found peripherally (i.e., where they are responsible for intestinal vagal afferent input) and centrally (i.e., in the chemoreceptor trigger zone and medullary vomiting center). Ondansetron has been used in veterinary medicine for approximately 8 years and has been anecdotally reported to stop vomiting in patients not responding to other commonly used antiemetics (e.g., puppies with parvoviral enteritis).

Ondansetron is metabolized by the liver. It is usually administered at 0.1 to 0.5 mg/kg IV q12-24h. In humans, it has the unusual characteristic of inhibiting emesis at low dosages, enhancing emesis at intermediate dosages, and then inhibiting emesis at higher dosages. The same has been shown for metoclopramide in humans. Dolasetron is metabolized into the active fraction (i.e., hydrodolasetron) by the ubiquitous carbonyl reductase. It is eliminated from the body by hepatic P-450 enzymes. It usually is administered to dogs and cats at 0.6 to 1 mg/kg, SC, IV, or PO q24h.

These drugs' antiemetic effects linger after the drug disappears from the blood. Therefore they need to be administered only once or twice daily. They are ultimately eliminated in the urine and bile. There is a wide margin of safety in humans, and side effects seem to be very rare in dogs and cats. Adverse effects in humans may include constipation, diarrhea, and somnolence. Prolongation of the QT interval is reported with dolasetron, but the importance of this in veterinary medicine is unknown and doubtful. These drugs have minimal interactions with other drugs. Ondansetron is reported to decrease the efficacy of tramadol.

It has been suggested that because there are many 5-HT$_3$ receptors in the GI tract, administering dolasetron orally might result in both a peripheral and a central antiemetic effect. Dolasetron is reported to have excellent bioavailability when given orally. Combining dolasetron and metoclopramide seems effective for chemotherapy-induced nausea in dogs and cats that is resistant to other antiemetics.[7]

182.6 NEUROKININ-1 RECEPTOR ANTAGONISTS

Maropitant is a centrally acting neurokinin-1 receptor antagonist that blocks the pharmacologic action of substance P in the CNS. Preliminary data suggest that it is a safe and effective antiemetic in the dog. It has recently been approved for use in dogs and is dosed at 1 mg/kg SC or 2 mg/kg PO q24h.[8]

182.7 ANTICHOLINERGIC AGENTS

Aminopentamide is an anticholinergic agent that has been used as an antiemetic in dogs. There are cholinergic receptors in the brain involved with the vomiting center and in the upper GI tract via the vagus nerve. The latter are muscarinic receptors. It is uncertain which receptors aminopentamide affects, but the drug appears to have relatively few of the typical side effects of anticholinergic agents on the GI tract (i.e., paralysis, distention). Clinically, it appears to be less effective than metoclopramide and certainly is less effective than the promazine derivatives and 5-HT_3 antagonists. Other anticholinergic medications (e.g., atropine, propantheline, glycopyrrolate) tend to be less effective or have more side effects (i.e., greater inhibition of GI motility), such that they are not generally recommended as antiemetics. Aminopentamide should be used with caution in animals with glaucoma, cardiomyopathy or tachyarrhythmias, hypertension, myasthenia gravis, or gastroesophageal reflux.

182.8 OTHER DRUGS

Trimethobenzamide has antidopaminergic properties but appears to be a relatively weak antiemetic in the dog. Steroids, especially dexamethasone, have been used to prevent nausea in humans undergoing chemotherapy or general anesthesia. There are limited data on the efficacy of this drug in cats,[6] but its common use and apparent effectiveness in vomiting cats with inflammatory bowel disease at least raises the question whether it has primary antiemetic efficacy. In humans, dexamethasone is primarily used as an antiemetic in combination with other drugs such as metoclopramide.

Based on the response of some patients with “limbic epilepsy” and sialomegaly, there is some question whether phenobarbital might have some antiemetic activity.[7] No studies clearly confirm or deny this possibility in dogs or cats.

182.9 PERIPHERALLY ACTING ANTIEMETICS

Drugs that soothe inflamed mucosal lesions (e.g., bismuth subsalicylate or barium sulfate) or relieve dyspepsia (antacid drugs) can be used to alleviate vomiting (see Chapter 181, Gastrointestinal Protectants). However, they are typically much less effective than the other drugs that have been discussed. 779 780

182.10 SUGGESTED FURTHER READING*

DM Boothe: Gastrointestinal pharmacology. In DM Boothe (Ed.): *Small animal clinical pharmacology and therapeutics*. 2001, Saunders, Philadelphia, *A veterinary text that describes the use of these drugs in dogs and cats*.

PJ Pasricha: Prokinetic agents, antiemetic drugs, and agents used in irritable bowel syndrome. In JG Hardman, LE Limbird (Eds.): *Goodman's and Gilman's the pharmacological basis of therapeutics*. ed 10, 2001, McGraw-Hill, New York, *A more detailed discussion of the mechanisms of vomiting and the pharmacologic properties of the various drugs*.

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* See the CD-ROM for a complete list of references.

183 Chapter 183 Neuromuscular Blockers

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183.1 KEY POINTS

- Neuromuscular blocking agents can be used to facilitate mechanical ventilation, improve gas exchange, and prevent respiratory dyssynchrony.
- Intermittent positive-pressure ventilation is mandatory with the use of neuromuscular blocking agents.
- Neuromuscular blocking agents do not have anesthetic or analgesic properties.
- Monitoring of blockade by train of four, peripheral nerve stimulation, and inspiratory effort is recommended.
- Nondepolarizing agents are the most commonly used neuromuscular blocking drugs.
- The effects of neuromuscular blocking agents can be reversed.

183.2 INTRODUCTION

Neuromuscular blocking agents are used to facilitate intermittent positive-pressure ventilation (IPPV) as part of a balanced anesthetic technique or as part of an anesthetic technique for animals undergoing intensive care mechanical ventilation. Neuromuscular blockade will help to prevent respiratory dyssynchrony, stop spontaneous respiratory efforts and muscle movement, improve gas exchange, and facilitate inverse ratio ventilation. [1] Neuromuscular blocking agents may also be useful in managing increased intracranial pressure and the muscle spasms of tetanus, drug overdose, or seizures.[1] Their use in surgery is to enhance skeletal muscle relaxation, to facilitate control of respiratory efforts during intrathoracic surgery, to immobilize the eye for ocular surgery, and to facilitate difficult intubation.[2]

These agents do not have anesthetic or analgesic properties, so it is imperative that they be given only when the animal is adequately insensible to pain and awareness.[3] Positive-pressure ventilation is mandatory with their use. The duration of action of neuromuscular blocking agents can be altered by hypothermia and acid-base and electrolyte disturbances, conditions commonly seen in critically ill patients. Neuromuscular blockers (NMBs) can be given by intermittent intravenous (IV) bolus or a constant rate infusion (CRI). Intermittent bolus administration may offer some advantages, including controlling tachyphylaxis, monitoring for accumulation, analgesia, amnesia, and limiting complications related to prolonged or excessive blockade.[1] There must be constant supervision when animals are receiving NMBs, because they are incapable of spontaneous respiration; should a malfunction of the mechanical breathing circuit occur, it would lead to death of the animal.

183.3 Neuromuscular Blocking Agents

The neuromuscular junction is made up of the motor nerve terminus, neurotransmitter acetylcholine, and the postsynaptic muscle end plate.[1] The impulse of an action potential causes the release of acetylcholine from the synaptic vesicles, which diffuses across the gap to the postsynaptic end plate.[1] The motor end plate contains the specialized ligand-gated nicotinic acetylcholine receptors.[1] The receptors convert the chemical signal into electrical signals, which leads to depolarization in the postsynaptic membrane of striated muscle.[1]

The two main classes of neuromuscular blocking agents are depolarizing and nondepolarizing. The depolarizing agent, succinylcholine, physically resembles acetylcholine and thus binds and activates the acetylcholine receptors.[1] There is initial muscle fasciculation followed by muscle relaxation.[3] Succinylcholine is metabolized by plasma cholinesterase, pseudocholinesterase.[3] In patients with azotemia, renal failure, severe liver dysfunction, or chronic debilitating disease, the decrease in plasma cholinesterase may lead to a prolonged blockade.[3] Succinylcholine is contraindicated with penetrating eye injuries, because it causes transient periocular muscle fasciculations that may increase intraocular pressure.[3] It should also be avoided in patients with myopathy, malignant hyperthermia, or in whom transient increases in abdominal or thoracic pressure are undesirable.[3]

The muscle fasciculations caused by succinylcholine are painful and can produce actual muscle injury with increased serum creatine kinase levels.[2] The drug can also affect heart rate and blood pressure, with the usual response being an increase in both, although in the cat there is an initial decrease in blood pressure followed by a slow rise. This can be prevented by prior administration of atropine.[2] Succinylcholine will increase serum potassium by 0.5 to 1 mEq/L because of its depolarizing effects, and this may result in unsafe levels in trauma patients.[3] For these reasons succinylcholine is not recommended for use in the critically ill patient.

183.4 NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

The preferred relaxant agent is the nondepolarizing NMB. Nondepolarizing agents bind to acetylcholine receptors but do not activate them; they act as competitive antagonists.[1]

There are two types of nondepolarizing NMBs, aminosteroidal and benzyl isoquinolinium compounds.

183.4.1 Aminosteroidal Compounds

Aminosteroidal compounds include pancuronium, vecuronium, and rocuronium.

Vecuronium is intermediate acting and a relatively noncumulative agent. It has minimal cardiovascular effects with a paralysis duration of approximately 25 minutes at a dosage of 0.05 to 0.1 mg/kg IV, with an onset time of 4 to 8 minutes.[2-4] Vecuronium can be repeated at 0.005 to 0.033 mg/kg IV or, if needed, can be given as a CRI of 1 to 1.7 µg/kg/min.[3,4] It undergoes renal elimination and bile excretion, so a prolonged effect may occur in patients with renal and hepatic compromise.[1] In the human literature vecuronium has been associated with prolonged blockade and when used with glucocorticoids may result in an increased risk of prolonged weakness when the vecuronium is discontinued.[1] In cats, metronidazole can potentiate the effects of vecuronium.[1]

Pancuronium has an onset of blockade in 2 to 3 minutes with a duration of 90 to 140 minutes.[1,3] It is dosed at 0.06 mg/kg IV and repeated at 0.03 mg/kg IV.[4] It does accumulate, and repeat dosing should be done cautiously.[3] Pancuronium is vagolytic and should be used with caution in patients that cannot tolerate an increase in heart rate, because it may lead to hypertension and tachycardia.[1,3] Pancuronium undergoes hepatic and renal metabolism and excretion, and this may make it less desirable for compromised patients.[2]

Rocuronium is 5 to 10 times more potent than vecuronium, with the shortest onset time and an intermediate duration.[5] A dosage of 0.4 mg/kg IV has been used in dogs anesthetized with halothane, which resulted in an onset of blockade in 98 ± 52 seconds and a duration of 32.3 ± 8.2 minutes.[5] Incremental doses of 0.16 mg/kg were used to prolong the blockade, and up to 7 increments were given that were noncumulative. The incremental doses produced a blockade of 20.8 ± 4.9 minutes in duration.[5] Rocuronium can be given as a CRI. Rocuronium is metabolized and excreted in a way similar to that of vecuronium, and the metabolite has only 5% to 10% of activity compared with the parent compound.[1,5]

183.4.2 Benzyl Isoquinolinium Compounds

The benzyl isoquinolinium compounds include atracurium, *cis*-atracurium, doxacurium, and mivacurium. Atracurium is intermediate acting, with minimal cardiovascular effects.[1] Atracurium is unusual in its degradation process in that it is independent of enzymatic function, it is inactivated in the plasma by ester hydrolysis and Hofmann elimination, and spontaneous degradation occurs at body temperature and pH.[1,3,6] Atracurium is indicated for use in neonates and patients with significant hepatic or renal impairment.[3]

Atracurium blockade occurs within 3 to 5 minutes and has a duration of 20 to 30 minutes.[3] Atracurium can be readministered at 0.1 mg/kg IV or given as a CRI of 3 to 8 µg/kg/min IV.[4] Recovery of normal neuromuscular activity usually occurs within 1 to 2 hours after discontinuing a CRI and is independent of organ function.[1] Long-term CRIs have been associated with tolerance, requiring dosage increases or switching to another NMB.[1] Atracurium can be used as part of an anesthetic induction technique. It may be considered when it is desirable to avoid increases in intraocular, intracranial, or intraabdominal pressure caused by coughing or a Valsalva maneuver.[3] It may also be used to provide faster control of ventilation in an unstable animal.[3]

There are two induction techniques. In one method, atracurium is given initially in divided doses of one tenth to one sixth of the calculated dose, and then 3 to 6 minutes later the rest of the calculated dose is given along with the induction agent.[3] This will accelerate relaxation after induction. The second technique is to give a single bolus of atracurium and 3 minutes later, at the onset of muscle weakness, give the induction agent.[3]

Side effects that may occur with atracurium include laudanosine formation and histamine release. Laudanosine is a breakdown product of Hofmann elimination that has been associated with CNS excitement.[1] This may be a concern in patients that have received extremely high doses or who have hepatic failure, because laudanosine undergoes liver metabolism.[1] At clinically useful doses, 0.1 to 0.3 mg/kg IV, the potential for histamine release does not appear to be a problem.[7]

Long-term use of atracurium and other NMBs has been associated with persistent neuromuscular weakness.[1] The potential for increasing the duration of the blockade may depend on what agents are used for sedation and anesthesia. Inhalant agents will increase the duration of the blockade in a dose-dependent manner.[7] There are some differences in this effect; isoflurane, desflurane, and enflurane have more potentiation than halothane, which in turn potentiates to a greater extent than nitrous oxide, barbiturates, opioids, or propofol.[7] A study in dogs with an NMB produced by atracuronium and anesthetized with either sevoflurane or propofol CRI demonstrated that the neuromuscular blockade was prolonged by approximately 15 minutes when using sevoflurane compared with propofol.[7]

cis-Atracurium is an isomer of atracurium. It has a similar duration, elimination profile, and production of laudanosine.[1] It produces few if any cardiovascular effects, has a lesser tendency to produce histamine release, and is more potent than atracurium.[1,6] As with atracurium, prolonged weakness may occur following long-duration use of *cis*-atracurium.[1] The dosage is 0.1 mg/kg, with incremental doses of 0.02 to 0.04 mg/kg IV in the dog, used to maintain the blockade.[6] The initial dose had a duration of 27.2 ± 9.3 minutes, the incremental doses appeared to be noncumulative, and no side effects were noted.[6] The kidney and liver excrete the metabolites of laudanosine, but the hepatic excretion is less important in the dog.[6] Laudanosine could cause hypotension and seizures, but this may be more likely in dogs with kidney or liver disease.[6] The higher potency of *cis*-atracurium means a lower dose is required, which results in lower metabolites levels.[6]

Mivacurium has been used in dogs. It consists of three isomers, cis-trans, trans-trans, and cis-cis.[8] The pharmacologically active isomers are cis-trans and trans-trans.[8] Mivacurium is metabolized by plasma cholinesterase and has the potential to cause histamine release.[9] In the dog anesthetized with thiopental and halothane, a dosage of 0.05 mg/kg IV had a significantly longer duration of action (180 minutes) than it did in humans, 24 minutes.[8] In a second study of dogs anesthetized with thiopental and halothane, comparing varying doses of mivacurium, 0.01, 0.02, and 0.05 IV, the onset of action and duration of effect were dose related.[9] Onset was 3.92 ± 1.70, 2.42 ± 0.53, and 1.63 ± 0.25 minutes, respectively, with the higher dose having the quicker onset.[9] The duration was also dose related, being 33.72 ± 12.73, 65.38 ± 12.82, and 151 ± 38.50 minutes, respectively, with the higher dose having the longest duration.[9] There was good hemodynamic stability in all dogs at all doses tested.[9] Mivacurium may be useful when long-term blockade is desirable.

Doxacurium has also been used in dogs. It had an extremely slow onset of action with a long duration of blockade in dogs anesthetized with isoflurane.[10] It is the most potent NMB available, with a potency 2 to 3 times that of pancuronium.[10] In dogs and cats it is not metabolized and is excreted unchanged in the urine and bile.[10] An animal with impaired renal function may have a more prolonged duration of blockade.[10] A dosage of 3.5 to 4.5 μg/kg IV had on onset time of 35 to 53 minutes, a duration of 81 to 158 minutes, and a recovery time of 29 to 51 minutes.[10] The long duration of action may be of benefit when considering the use of NMB for long-term mechanical ventilator use.

183.5 MONITORING OF BLOCKADE

A peripheral nerve stimulator is recommended for monitoring neuromuscular blockade. Monitoring the depth of the blockade will allow the lowest dosage to be used and therefore minimize adverse effects.[1] It will also help to confirm that adequate neuromuscular function has returned before removal of ventilatory support and anesthesia.[3] Monitoring is done by observing skeletal muscle movement and respiratory efforts and measuring the twitch response to a transcutaneous delivery of electric current to induce a peripheral nerve stimulation.[1] A peripheral motor nerve is stimulated to produce a propagated action potential by sufficient current density via the stimulator.[2] This is achieved by the negative electrode of the stimulator being placed closest to the nerve and the positive electrode placed a short distance away.[2] After the nerve has been stimulated and depolarized to produce an action potential, it is resistant to further stimulation for the refractory period of 0.5 to 1 millisecond.[2]

The peripheral nerves most commonly used include the facial, ulnar, tibial, and superficial peroneal.[2] The peroneal nerve is found on the lateral aspect of the tibia, just distal to the lateral condyle, and innervates the extensor muscles of the hind foot.[3] The facial nerve crosses the masseter muscle and courses ventral to the eye, and innervates the muscles of the muzzle.[3] The ulnar nerve is along the medial aspect of the elbow and innervates the flexor muscles of the front foot.[3] When the nerve is stimulated, the foot or muzzle should twitch. Train of four (TOF) employs a sequence of four stimuli at 0.5-second intervals, 2 Hz, using a 30- to 50-mA stimulus. It can be repeated every 12 seconds if needed.[2,3] A normal TOF should be evaluated before the administration of an NMB. After the NMB has been given, the TOF is monitored serially.

The strength of the twitch response is directly related to the number of postjunctional receptors occupied by the NMB.[3] With use of a nondepolarizing NMB, the twitches will fade in intensity and there is a decrease in twitch height.[3] Fade, the increased depression of successive twitches, is due to the NMB acting on prejunctional receptors and interfering with mobilization.[3] The TOF ratio, the ratio of the twitch height of the fourth to first response can be evaluated; a TOF ratio greater than 0.5 is generally accepted as being compatible with a clinically safe recovery.[2] A TOF ratio of 0.8 to 0.9 would be preferred to avoid missing potential residual muscle weakness.[2] The fourth twitch is as strong as the first when 25% to 30% of the receptors are free of the blocking drug.[2] In human intensive care patients on mechanical ventilation, the TOF was monitored with a goal of maintenance of one to two twitches.[1]

Monitoring the depth of sedation and anesthesia is more difficult when using neuromuscular blockade, because the normal neuromuscular reflex parameters, jaw tone, palpebral, and spontaneous movements, are blocked. Heart rate, blood pressure, mucous membrane color, and pulse strength need to be monitored closely. An increase in heart rate and blood pressure that cannot be attributed to hypovolemia, hypoxia, hypercarbia, drugs, or hypotension may be indicative of insufficient sedation or anesthesia. Additional reflexes such as lacrimation, salivation, slight muscle movement of limbs or face, and curling the tip of tongue may signal awareness or pain perception.[3] If the animal does awaken, administration of intravenous anesthetic agents, such as propofol, thiopental, diazepam, and ketamine, or an increase in the level of inhalant anesthetic or intravenous analgesic, such as an opioid, should be considered.

183.6 RECOVERY FROM NEUROMUSCULAR BLOCKADE

When NMB effects begin to diminish, the animal may show a decreased chest wall compliance and increased resistance to ventilation; there will be greater peak inspiratory pressure generated at the same tidal volume.[3] Nystagmus, papillary dilation, and palpebral reflex may be noted. To evaluate the recovery from neuromuscular blockade, assess the tidal volume using a Wright respirometer, the character of ventilation, the ability to swallow, pulse oximetry, and end-tidal carbon dioxide levels. If there is residual weakness, this can be serious and potentially life threatening. If the strength of recovery is in doubt, a reversal agent can be given.

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183.7 REVERSAL

Reversal of nondepolarizing agents is possible, although not always necessary. Reversal may be considered in the critically ill patient to improve respiratory muscle function.[3] Anticholinesterase inhibitors, edrophonium or neostigmine, are used for reversal. They reduce the breakdown of acetylcholine by cholinesterase, resulting in acetylcholine accumulating at the neuromuscular junction and at other body sites.[2,3] Reversal should not be attempted when there are no twitches seen with the TOF monitor. A minimum of 10% of control twitch height must be present for reversal to be successful.[3]

Accumulation of acetylcholine will also produce muscarinic effects such as bradycardia, salivation, increased bronchial secretion, smooth muscle contraction, defecation, urination, and hypotension.[2,3] These side effects can be minimized by concurrent administration of an anticholinergic drug such as atropine or glycopyrrolate.

Neostigmine has peak effects at 7 to 10 minutes, with a duration of 60 to 70 minutes, and is given at 0.04 to 0.06 mg/kg IV, combined with glycopyrrolate 0.01 mg/kg IV to combat bradycardia.[3,4] Glycopyrrolate is commonly used with neostigmine, because the two drugs have similar times of onset and duration. Serious cardiac arrhythmias can occur if the carbon dioxide has been allowed to accumulate at the end of the procedure with the view that this will stimulate respiration.[2] Hypercapnia also increases the neuromuscular block of nondepolarizing agents and therefore antagonism is less likely to be effective with a high carbon dioxide level.[2] Neostigmine undergoes hepatic metabolism and renal elimination, and the effects may be prolonged in patients with renal failure.[3]

Edrophonium has peak effects within 1 to 2 minutes and a duration of approximately 66 minutes. Dosage is 0.5 mg/kg IV, and it is combined with atropine 0.01 to 0.02 mg/kg IV.[3] It is combined with atropine because they have similar times of onset and duration. The atropine should be given 5 minutes before the edrophonium.[4] Edrophonium is metabolized by the liver, and it will have prolonged effects in patients with renal failure and hepatic failure.[3]

183.8 POTENTIAL ADVERSE EFFECTS

There are potential adverse effects with the use of neuromuscular blockade. Skeletal muscle weakness can be a problem with prolonged use of NMBs in an intensive care setting. This can be the result of prolonged paralysis following discontinuation of the NMB and is primarily due to accumulation of the NMB or metabolites.[1]

A condition reported in the human literature is called *acute quadriplegic myopathy syndrome* (AQMS). It manifests with a clinical triad of acute paresis, myonecrosis with increased creatine phosphokinase concentration, and abnormal electromyography.[1] The electromyelogram is characterized by severely reduced compound motor action potential amplitudes and evidence of acute denervation.[1] There is neuronal dysfunction and later, days to weeks, muscle atrophy and necrosis may develop.[1] There may be an association of neuromuscular blockade concurrent with glucocorticoid administration and development of AQMS.[1] Afflicted patients manifest acute, diffuse, flaccid weakness and an inability to be weaned from the ventilator, although sensory function generally is preserved.[1] Experimental studies have been done in animals, showing that denervation for longer than 24 hours induces profound negative nitrogen balance and increases expression of steroid receptors in muscle.[1] The denervation sensitizes muscle to even normal glucocorticoid concentrations, and evidence suggests that the combination of denervation and high-dose glucocorticoids precipitates myosinolysis.[1]

Drugs that potentiate the action of NMBs include local anesthetics, lidocaine, aminoglycosides, polymyxin B, tetracycline, procainamide, quinidine, magnesium, calcium channel blockers, β-adrenergic blockers, cyclophosphamide, cyclosporine, dantrolene, diuretics, and lithium carbonate.[1] Phenytoin, carbamazepine, theophylline, and ranitidine antagonize the actions of NMBs.[1]

Patients that are receiving NMBs also need to be watched for deep vein thrombosis and should receive physical therapy to maintain joint mobility.[1] They are at risk for developing keratitis and corneal abrasions; therefore prophylactic eye care with eye drops or ointment to provide lubrication and keeping the eyes closed is recommended.[1]

It is possible that with long-term use of neuromuscular blockade the animal may develop tachyphylaxis to the agent. If blockade is still required, another NMB should be used.[1] It is advisable to use neuromuscular blocking agents for the shortest time possible. Special conditions in which there are fewer acetylcholine receptors, such as with myasthenia gravis, will lead to an increase in sensitivity to nondepolarizing NMB.[1] If there is a long-term decrease in acetylcholine release, the number of acetylcholine receptors within the muscle increases.[1] This will lead to a resistance to the nondepolarizing NMB and require that more receptors be blocked to achieve the desired effect.[1]

183.9

SUGGESTED FURTHER READING*

VM Lukasik: Neuromuscular blocking drugs and the critical care patient. *J Vet Emerg Crit Care*. **5**, 1995, 99, *A nice review of NMBs used in critically ill animals*.

MJ Murray, J Cowen, H DeBlock, et al.: Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med*. **30**, 2002, 142, *An excellent review of the use of NMBs in critically ill patients, but this review is for the human patient.*

* See the CD-ROM for a complete list of references

184 Chapter 184 Narcotic Agonists and Antagonists

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184.1 KEY POINTS

- Opioids are an important class of drugs for critically ill veterinary patients because of their efficacy and relative cardiovascular safety.
- Opioids are most commonly used for analgesia, but may also be prescribed for antitussive or sedative therapy.
- The most commonly used analgesics include morphine, fentanyl, hydromorphone or oxymorphone, buprenorphine, and butorphanol.
- It is important that the veterinarian understand the various opioids' clinical efficacies, potencies, and potential side effects before using them.
- Opioid antagonists include naloxone, nalmefene, and naltrexone. Butorphanol and nalbuphine commonly are used for partial reversal of pure μ-agonist drugs.

184.2 INTRODUCTION

Opioids serve a variety of roles in veterinary critical care. The foremost of these is as the foundation of analgesic therapy, but they are also used for their sedative and antitussive effects. Less frequent applications may include supporting right heart function and control of compulsive behaviors. In the past, opioids were also used to decrease gastrointestinal (GI) motility.

As analgesics, the opioids are the first line of defense in managing pain due to injury and disease. The remarkable cardiovascular sparing effects and inherent safety of opioid therapy in critically ill patients are prominent advantages of this class of drugs. Opioids anchor contemporary balanced or multimodal strategies for pain management. Although this chapter deals specifically with the opioids, other publications extend the topic of analgesia in critical care to encompass complementary classes of analgesic drugs and other approaches to pain management.[1,2]

184.3 TERMINOLOGY AND HISTORY

184.3.1 Opium

At least 20 distinct alkaloids are derived from juice of the poppy. Among these, the phenanthrenes are represented by morphine and the benzylisoquinoline derivatives by papaverine.

184.3.2 Opiate

The term *opiate* specifically refers to drugs derived from opium. The first of these was morphine, isolated and recognized in 1803 as the active ingredient in laudanum by Friedrich Wilhelm Adam Ferdinand Serturner, an assistant apothecary. This contribution has been recognized as the beginning of the modern era of pharmacology.

184.3.3 Opioid

The term *opioid* is a more precise, yet broadly inclusive, term for synthetic as well as opium-derived compounds that bind specifically to several opioid receptors and thereby have some morphine-like effects.

184.3.4 Narcotic

The word *narcotic* was derived from a Greek term for sleep or stupor. Because this group of compounds does not readily and reliably produce sleep in all veterinary patients, it is a less than appropriate descriptor in veterinary medicine. Law enforcement organizations may refer to many substances with a potential for diversion and abuse as *narcotics*. This inclusion of opioid and nonopioid controlled substances can lead to confusion. Controlled substances, including the opioids, must be kept secure under lock and key. Accurate and appropriate inventory is required, with the level of control for each drug related generally to the relative potential for abuse.

184.4 STRUCTURE ACTIVITY RELATIONSHIP

The phenanthrene opioid compounds have a three-ring nucleus and a piperidine ring structure with a tertiary amine nitrogen. The levorotatory forms are much more active agonists than the dextrorotary forms.

184.5 MECHANISM OF ACTION

Opioids bind to stereospecific Opioid Receptors located most notably in the central nervous system (CNS), but also in many other sites throughout the body. The receptor affinity correlates well with analgesic potency for the opioids classified as pure agonists only. Receptor binding of endogenous or exogenous legends activates G proteins as second messengers, modulates adenylate cyclase activity, and thereby alters transmembrane transport of effectors. Opioids also interfere presynaptically with the release of neurotransmitters. These changes result in interruption of the pain message to the brain and a decreased sensation of pain within the brain. Opioids do not alter the responsiveness of afferent nerve endings to noxious stimuli, nor do they impair conduction of nerve impulses along peripheral nerves.

184.6 OPIOID RECEPTORS

There are a variety of opioid receptors and subtypes of receptors within many locations in various tissues. Differential binding and activation at specific receptors (μ-receptors, κ-receptors, and δ-receptors) and locations serve to mediate the spectrum of opioid effects.

184.7 PHYSIOLOGIC EFFECTS OF OPIOIDS

Occupation of CNS receptor sites by opioids produces analgesia, sedation, muscle relaxation, and behavior modification. The CNS depressant action of the opioids results from their effects on the cerebral cortex. In contrast to the more typical sedation and narcosis produced in human patients, disorientation and excitement may also occur in veterinary patients receiving opioid therapy. The excitatory behavioral activity results from effects of the drug on the hypothalamus. The ability of the opioids to cause depression or excitement is highly drug and species dependent. Excitatory responses may be linked to an indirect activation of dopaminergic receptors. The major tranquilizers, the benzodiazepines and phenothiazines, can block this activation.

Combinations of some opioids and tricyclic antidepressants can produce hypotension. Meperidine, and occasionally other opioids, when administered to patients receiving monoamine oxidase inhibitors (e.g., selegiline, L-deprenyl [Anipryl]) can result in rare but severe and immediate reactions that include excitation, rigidity, hypertension, and severe respiratory depression.

Opioids can be potent respiratory depressants, depressing both respiratory rate and tidal volume. Although this is rarely a clinically significant problem in healthy patients, special attention is warranted in critically ill patients. Animals with increased susceptibility to respiratory effects include those with underlying airway obstruction (e.g., brachycephalic animals) and those with pulmonary disease. The opioids directly depress the pontine and medullary respiratory centers. They also produce a delayed response (altered threshold) and decreased response (altered sensitivity) to arterial carbon dioxide, leading to retention of carbon dioxide. Tachypnea is sometimes observed after narcotic administration and may be due to excitation and/or alteration of the thermoregulation center. Panting in dogs is most notable with oxymorphone and hydromorphone administration.

Bronchoconstriction may also occur. A rare and incompletely understood complication of opioid therapy is a phenomenon known as “wooden chest.” With this syndrome, the patient's chest wall muscles become spastic, making ventilation difficult. Treatment involves reversal of the opioid drug and, if necessary, muscle relaxant therapy.

At therapeutic dosages, the opioids have minimal effects on the cardiovascular system. There is little or no change in blood pressure and myocardial contractility. The opioids can produce a bradycardia that is responsive to atropine or other anticholinergic agents. Decreased heart rate is vagally mediated and a manifestation of relieved pain. The opioids affect the ability of the vascular system to compensate for positional and blood volume changes, although orthostatic hypotension is presumably more problematic in bipedal than quadrupedal patients. Among the opioids, both morphine and meperidine can cause histamine release, leading to marked hypotension. To minimize histamine-related complications following intravenous administration of morphine, the drug should be diluted with saline and the injection given slowly over 10 to 20 minutes.[1,3] Morphine and meperidine are contraindicated in patients with mast cell tumors or other histamine-based diseases. Other opioids are much less likely to cause significant histamine release.

A variety of other physiologic effects may be of interest in the critical care setting. The opioids produce an initial stimulation of the GI tract (vomiting, defecation, or both) followed by a decrease in motility. Most opioids cause release of antidiuretic hormone. Urine retention due to bladder atony is an infrequent, but clinically significant, problem in some animals receiving opioid therapy. Bladder emptying should be verified in all patients.

Some animals receiving opioids may unexpectedly over-respond to noises or sensory stimuli. When this occurs, it can contribute to dysphoria and increase stress in the critically ill patient. The importance of a quiet and calming environment is recognized, but this is challenging to achieve in many critical care settings. Placing cotton balls in the ears may help to alleviate the noise sensitivity.

Decreased body temperature may be observed with opioids because the thermoregulatory center in the hypothalamus is reset to a lower setting. Panting in dogs is one manifestation of altered body temperature regulation. Alternatively, significant increases in body temperature occasionally occur after opioid administration. This appears to be most common in cats and somewhat drug and dosage dependent. Cats receiving higher-than-usual clinical dosages of morphine, meperidine, and hydromorphone frequently developed increased body temperature (40° to 41.7° C or 104° to 107° F) in one study. Buprenorphine did not result in hyperthermia in feline clinical or research models.[4]

184.8 METABOLISM AND EXCRETION

Metabolic elimination of opioids is accomplished by hepatic conjugation and metabolite excretion in the urine. The principal metabolites can be highly active, as in the case of morphine in humans. In the case of meperidine, the metabolite normeperidine is a convulsant. Extended therapy with meperidine can lead to neurotoxicity and seizures. Opioid overdoses can effectively change the kinetics of elimination from “first order” to “zero order” by saturating the processes responsible for elimination, thereby greatly prolonging the duration of action. This is perhaps most notable with large overdoses of butorphanol, which lead to prolonged sedation but cause little increase in the magnitude of sedation or analgesia as a result of the “ceiling effect” seen with this agonist-antagonist opioid. Independent of any conditions altering elimination, the duration of action of the clinically useful opioids ranges widely, from 0.5 to 8 hours.

184.9 EPIDURAL OPIOIDS

Spinal or epidural (neuroaxial) opioid analgesia has been well described and proven effective in veterinary medicine. Epidural morphine analgesia is widely used and is increasingly popular as a method for providing long- 785
lasting profound analgesia. The systemic side effects of the opioids are often substantially decreased, making this 786
technique especially useful in critically ill animals. The technique is rather simple, easily accomplished with basic clinical skills, and can be very cost effective for providing substantial analgesia. Preservative-free morphine (e.g., Duramorph), designed for epidural use, is the best-recommended product. Buprenorphine, hydromorphone, and oxymorphone are also used.

Table 184-1 Relative Potencies of Opioids

Opioid	**Relative Potency**
Morphine	1
Methadone	1
Meperidine (Demerol)	$\frac{1}{5}$
Codeine	$\frac{1}{10}$
Butorphanol (Torbugesic)	3 to 5
Nalbuphine (Nubain)	0.5 to 0.9
Hydromorphone (Dilaudid)	10
Oxymorphone (Numorphan)	10
Buprenorphine (Buprenex)	50 to 100
Fentanyl (Sublimaze)	100 to 150
Pentazocine (Talwin)	⅓
Etorphine (M-99)	1000 to 80,000

A relatively small dose of morphine (0.1 mg/kg) is administered by epidural injection after induction of general anesthesia or with heavy sedation. Effective pain relief begins within approximately 30 minutes and persists for 12 to 24 hours. Addition of a local anesthetic, typically bupivacaine (0.5 mg/kg), to the epidural injection further conveys a blunting of deleterious postoperative or injury-associated increases in stress hormones and the metabolic response to surgery. An epidural catheter can also be placed to provide repeated dosing or a constant rate infusion (CRI) into the epidural space (see Chapter 164, Analgesia and Constant Rate Infusions). Contraindications to epidural injection or catheter placement include local infection, coagulopathy, neurologic dysfunction, marked obesity (increased difficulty), and hypovolemia with hypotension (avoid the local anesthetics or compensate with IV fluids for volume expansion).

184.10

POTENCY AND EFFICACY OF OPIOIDS

The relative potency of opioids is compared with that of morphine on an “equal-analgesic basis” (Table 184-1). For the pure-agonist opioids, maximum biologic effect (e.g., analgesia or respiratory depression) is relatively dosage dependent. The relative potency and the relative lack of efficacy of butorphanol, typically classified as a mixed agonist-antagonist opioid, provide an excellent example of the difference between efficacy and potency. Clinical efficacy helps identify useful medications for a specific purpose, and potency helps define dosage within the limits of efficacy. Recommended dosages of several opioids for critical care analgesia are listed in Table 184-2. Dosage ranges are broad for the opioid analgesics, and titration to achieve the desired effect is needed to care for this group of medically challenged patients.

184.11 CHARACTERISTICS OF CLINICALLY USEFUL OPIOIDS

184.11.1 Morphine

Morphine, a pure-agonist opioid, is not only the standard of comparison with other opioids, but remains one of the most useful analgesic medications. Morphine confers sedation in addition to analgesia and both effects are both dosage dependent, reliable, and effective in many clinical settings. Vomiting, diarrhea, and bradycardia may occur, but these are seen less commonly when morphine is given to treat existing pain than when given in the absence of pain. Vomiting may also be less common when diluted morphine is injected slowly intravenously rather than following intramuscular or subcutaneous injection. There is rapid absorption and almost complete bioavailability of morphine administered by either subcutaneous or intramuscular injection.[5] Dosage recommendations do not differ with the route of injection.

When possible, opioids should be administered by intravenous, rather than intramuscular or subcutaneous, injection to reduce trauma and stress in critically ill patients. Hypotension and bronchoconstriction occur in some patients as a result of histamine release, especially in dogs and following intravenous administration. Morphine is contraindicated in patients with mast cell tumors or other histamine release abnormalities (see previous section Physiologic Effects of Opioids).

CRI of morphine or morphine plus other analgesics is very useful in the treatment of critical care patients experiencing pain. The relatively long plasma half-life of morphine can lead to an increasing plasma concentration when given as a CRI. This potential problem is minimized by adjusting the infusion as needed to balance analgesia and sedation. The CRI becomes an adjustable rate infusion, with drug dosage titrated to the desired effect. The use of neuroleptanalgesia (an opioid combined with an anxiolytic drug) or the mixture of morphine, lidocaine, and ketamine delivered as a CRI is effective in many patients.[1,6] One of many recipes for the latter cocktail is given below.

Morphine-lidocaine-ketamine CRI:

1 Remove 72 cc from a 1-L bag of saline or balanced electrolyte fluids.

2 Add 68 cc of 2% lidocaine, 4 cc morphine (15 mg/mg), and 0.6 cc ketamine (100 mg/ml).

3 Begin CRI at 1 to 2 cc/kg/hr.

4 Adjust as needed for comfort and sedation.

Oral administration of morphine may be effective in some dogs, but the drug is poorly and erratically absorbed from the GI tract.[7] Individual variability in bioavailability following oral dosing suggests that either the oral route is not to be recommended or, at least, requires individual assessment of pharmacodynamics and biologic effectiveness.

184.11.2 Methadone

Methadone acts similarly to morphine in small animals with regard to its degree of analgesia and duration of effect. It is a μ-receptor agonist that also noncompetitively inhibits N-methyl-D-aspartate (NMDA) receptors. It is more lipid soluble than morphine, but causes less sedation and vomiting.

Table 184-2 Opioid Analgesics and Recommended Dosages

Drug	Dosage	Duration	Indications	Side Effects	Comments
Morphine	*Dog:* 0.5 to 1 mg/kg IV, IM, SC IV CRI: 0.05 to 0.5 mg/kg/hr, reduce 50% after 24 hours *Cat:* 0.05 to 0.2 mg/kg IV, IM, SC IV CRI: 0.025 to 0.1 mg/kg/hr, reduce if agitation develops	4 to 6 hr	Sedation accompanying analgesia	Vomiting, diarrhea, and bradycardia may occur Hypotension and bronchoconstriction possible (histamine release, with rapid IV use)	Dilute with saline for slow intravenous injection
Hydromorphone (or oxymorphone)	*Dog:* 0.0 to 0.1 mg/kg IV, IM, SC IV CRI: 0.01 to 0.05 mg/kg/hr *Cat:* 0.05 to 0.1 mg/kg IV, IM, SC IV CRI: 0.01 to 0.025 mg/kg/hr, reduce if hyperthermia or agitation develops	4 hr	Useful for managing substantial pain	Panting, vomiting, diarrhea, bradycardia, dysphoria may occur Dosage-dependent sedation or excitement, hyperthermia in cats	—
Fentanyl	*Dog and cat:* 2 to 10 μg/kg/hr as a CRI after IV loading dose of 2 to 10 μg/kg	Rapid onset and short duration	Excellent for procedural uses and as a CRI for sustained and titratable analgesia in critical care	Dysphoria	Reduce dosage if hyperthermia or agitation develops (cats more susceptible) May be combined with lidocaine CRI (see text)
Methadone	*Dog:* 0.1 to 0.5 mg/kg IV *Cat:* 0.05 to 0.25 mg/kg IV (up to two times dose if given IM or SC)	4 to 6 hr	Sedation accompanying analgesia	Vomiting, diarrhea, bradycardia	Causes less sedation and vomiting than morphine

Butorphanol (Torbutrol, Torbugesic, Stadol)	*Dog:* 0.1 to 0.5 mg/kg IV, IM, SC *Duration:* 1 to 2 hr (analgesic effect) IV CRI: 0.1 to 1 mg/kg/hr *Cat:* same as for dog, except for a longer duration of action, 2 to 4 hr IV CRI: 0.1 to 0.5 mg/kg/hr	See column to left	Ceiling effect, limited analgesia, useful for mild sedation Antitussive action (often desirable) Minimal systemic effects	Partial opioid reversal	—
Nalbuphine (Nubain)	*Dog and cat:* 0.2 to 4 mg/kg IV, IM, SC	30 to 60 minutes	Minimal analgesia and minimal sedation Used in combination with sedatives or tranquilizers	Partial reversal of μ-agonist opioids	—
Buprenorphine (Buprenex, Temgesic)	*Dog and cat:* 0.005-0.002 mg/kg IV, IM, SC	Slow onset and long duration of effect (6 to 8 hr)		Some ceiling effect on respiratory depression Vomiting not commonly seen	*Cat:* Oral absorption excellent, alternative to injection

Rates for intravenous CRI taken from Hansen BD: Analgesia and sedation in the critically ill, *J Vet Emerg Crit Care* 15:285, 2005, as recommended analgesic drug doses used as fluid additives in critical care.

CRI, Constant rate infusion; *IM,* intramuscular; *IV,* intravenous; *SC,* subcutaneous.

Dosages taken from the literature and the author's experience.

184.11.3 Hydromorphone and Oxymorphone

Hydromorphone is also a pure-agonist opioid. Vomiting and diarrhea are associated with it less frequently than with morphine, but panting is frequently seen in dogs. Hydromorphone does not stimulate histamine release. There may be less excitement or dysphoria than with morphine, but the literature and anecdotal reports are mixed on this subject. Hyperthermic reactions occasionally may be seen in cats receiving hydromorphone. This is a very useful opioid for managing substantial pain and is quite similar to the formerly popular opioid, oxymorphone.

184.11.4 Fentanyl

Fentanyl has been a useful opioid in veterinary medicine for many years. Combined with droperidol to form Innovar-Vet, fentanyl was used as a component of this once-popular neuroleptanalgesic. More recently, fentanyl formulated in a controlled-release transdermal patch for human pain treatment has been used (extralabel) in many veterinary species. The pharmacokinetics and pharmacodynamics of transdermal fentanyl have been described for many species, including dogs and cats. This formulation is useful for sustained analgesia in animals with significant trauma (e.g., multiple fractures after vehicular trauma), as a portion of the treatment of postoperative pain, for critically ill animals with painful systemic disease (e.g., pancreatitis), and in some cancer patients. Fentanyl patches can be very useful in cats as well as in dogs. Breakthrough pain may require a supplemental analgesic strategy, often with a complementing class of nonopioid analgesic.

The fentanyl patches are sold as Duragesic from Janssen (Titusville, NJ). They are available in various rates of drug delivery: 25, 50, 75, and 100 μg/hr. Effectiveness has been reported for 50-μg patches in small and medium-sized dogs. The 25-μg patches have been used extensively in cats and dogs weighing less than 5 kg. The behavioral effect of dysphoria and dementia is unacceptable in some animals, which may require tranquilization or removal of the patch. Uncovering only one half of the barrier layer before application has been used to reduce the dosage and minimize this problem, particularly in smaller dogs and cats.

Patches are applied to clipped skin. Uptake is somewhat variable among patients and clinical efficacy may be related, in part, to differences in uptake of fentanyl. Onset of analgesia requires 12 to 24 hours after application of the patch. Hence, other options, such as injectable opioid or other medications, should be used initially to provide analgesia. It is important to prevent the patient from damaging or ingesting these patches or the contents. Of note, application of a heating pad can greatly increase uptake of the drug, with significant overdose possible. Duration of effectiveness is roughly 4 days.

Fentanyl can be a highly abused opioid, and there have been reports of clients removing fentanyl patches from their animals for drug abuse or diversion purposes. Some clinicians will use the patches only for hospitalized, closely observed patients. Others find the fentanyl patches a very useful part of managing cancer pain in outpatients, including the terminally ill. The patch can help provide a steady level of opioid for a prolonged period in a way that is cost effective and reasonably convenient for clients. It is essential to emphasize the potential dangers and importance of protecting other pets and children from ingestion or other possible exposures. Expended (used) patches still contain fentanyl and should be handled with care.

Injectable fentanyl has such a short duration of action that a bolus dose, by itself, is of limited benefit for treatment of prolonged (e.g., postoperative) pain but may be excellent as a component of procedural pain management (e.g., for bone marrow aspiration or sedation or analgesia for other diagnostic procedures such as radiography). The rapid onset and short duration of injected fentanyl makes it an excellent choice as a CRI for sustained and titrated analgesia in critical care. For dog and cats, a 2 to 10 μg/kg/hr IV CRI is initiated after an IV loading dose of 2 to 10 μg/kg. As a CRI, fentanyl (50 μg/ml) may be combined with an equal volume of 2% lidocaine as follows: 0.1 to 0.3 ml/kg/hr of a 1:1 mixture (by volume) of fentanyl and lidocaine can be given as needed for comfort and sedation.

184.11.5

Butorphanol

Butorphanol was first available in veterinary medicine as an antitussive medication. It can be a useful sedative and analgesic in critical care and is compatible in combinations with many nonopioid analgesics and sedatives. For mild analgesia and a sedative contribution, butorphanol can be useful in critical care. Recognizing the existence of a “ceiling effect” limiting analgesic efficacy of this mixed-acting agonist/antagonist opioid, butorphanol has been overused inappropriately to the exclusion of the more effective μ-agonist medications. In many cases a pure-agonist opioid, such as morphine, hydromorphone, or fentanyl, should be selected for more effective analgesia. The analgesic actions of butorphanol are limited not only by its mild contribution to pain relief but also by its duration of effect, particularly in dogs. A CRI of butorphanol may be more effective for sustained analgesia in dogs and cats.

Because the “ceiling effect” with butorphanol also limits respiratory depression, there is less potential for reflexive increases in intracranial pressure (ICP). For patients with cranial trauma, or those that for other reasons are at risk of ICP or increased intraocular pressure, this decreased potential for respiratory depression can add safety. Vomiting is rarely a feature of the drug, thereby preventing another risk factor for increases in ICP or intraocular pressure.

Used for partial reversal of μ-agonist opioids, butorphanol can provide for a gentle reversal of excessive μ-agonist–mediated depression (or dysphoria in cats), yet maintain some quality of analgesia and sedation.[8] In this manner, as an alternative to naloxone, it can serve as a very useful partial antagonist in critical care.

184.11.6 Nalbuphine

Much like butorphanol, nalbuphine is a weak analgesic that is usually classified as a mixed agonist-antagonist opioid. The sedation provided by nalbuphine is minimal, but it contributes to the sedation afforded by simultaneously administered tranquilizers or sedatives. Nalbuphine is used in combination with acepromazine, benzodiazepines, or α_2-agonists. Inadequate analgesia and minimal contribution to sedation are both substantial limitations to the value of nalbuphine. As with butorphanol, nalbuphine can be used for partial reversal of μ-agonist opioids. Nalbuphine is not a scheduled drug.[9]

184.11.7 Buprenorphine

Buprenorphine typically has been classified as a partial-agonist opioid, with limited agonist activity at μ-receptors. Research suggests that the “ceiling effect” with this drug may apply more to respiratory depression than to its analgesic actions. As such, its analgesic efficacy is relatively great. The duration of analgesic action is greater than that of any other clinically available opioids (with the exception of controlled release formulations and neuroaxial routes of administration). Buprenorphine, like butorphanol, does not stimulate vomiting and similarly may be a good choice for the patient at risk of increased ICP or IOP. In cats, but not dogs, buprenorphine has excellent bioavailabilty from the oral mucosa. Transmucosal (oral or sublingual) administration of the injectable product is well tolerated and provides a convenient noninjectable option for relatively long-lasting substantial analgesia in cats.[10] 788 789

184.11.8 Tramadol

Tramadol provides a mild opioid-like, NSAID analgesic effect. There is slight μ-opioid binding activity, but the analgesic action is attributed more to interference with both serotonin storage and norepinephrine reuptake. Analgesic action exceeds μ-receptor binding characteristics. The principal metabolite has greater mu binding than does the parent compound. Tramadol may be effective when a weak opioid such as codeine would be chosen. It is available only as an oral medication, which might limit its use in critically ill patients.

184.11.9 Codeine

Codeine has one-tenth the potency (analgesic properties) of morphine. It is available only as an oral formulation (limiting its use in the intensive care unit) and is readily absorbed from the GI tract. Codeine is a potent oral analgesic for dogs that require long-term administration (e.g., as a component of cancer pain management).

184.11.10 Opioid Antagonists: Naloxone, Nalmefene, Naltrexone

Three significant opioid antagonists are naloxone (very short acting), nalmefene, and naltrexone (both long acting). These compounds bind with great affinity to the μ, κ, and σ opioid receptors, competitively displacing agonists with lesser affinity and thereby reversing actions of the agonist agents. The antagonists convey no analgesic activity. Naloxone has been primarily for reversal of opioid agonist effects, but also used experimentally in the treatment of shock in dogs.[11] With the infusion of high doses of naloxone in a model of hypovolemic shock, splanchnic capacitance was reduced leading to an improvement in venous return and cardiac output.

In displacing morphine and other opioids from receptor sites, the antagonist can reverse all opioid effects. Sedation, respiratory depression, and analgesia can be reversed abruptly, precipitating acute reactions of severe pain, excitement, and profound stress. If naloxone is to be used for reversal of adverse or excessive opioid agonist effects in a critical care setting, the diluted drug should be given slowly by IV infusion to effect. Patients should be observed for relapse into sedation or for a return of adverse effects (renarcotization). It is difficult to titrate opioid reversal in order to arouse a patient from excessive sedation and still preserve analgesia.

Partial reversal using butorphanol or nalbuphine is an alternative approach that is suitable for many patients. Buprenorphine binds with great affinity to the receptors and can be difficult to reverse. Fortunately, few critical care patients require complete opioid reversal. Supportive care and treatment of opioid-induced sedation or excessive side effects with partial reversal agents are generally recommended.

Nalmefene and naltrexone (long duration of effect) similarly compete for opioid receptors, displacing agonist, both exogenous and endogenous. As such, these have been used to treat compulsive behavior disorders. The lack of any significant naltrexone metabolite, in dogs relative to humans, might limit the efficacy of this strategy.[12]

184.12 CONCLUSION

Opioids are among the safest as a class of analgesic medications, with profound usefulness in the critical care setting. Pain relief is the most significant application of the opioids, but they also offer sedation and cough suppression. The variety of opioids and the variety of administration routes and strategies available allows for creative application to the benefit of critically ill veterinary patients.

184.13 SUGGESTED FURTHER READING*

BD Hansen: Analgesia and sedation in the critically ill. *J Vet Emerg Crit Care*. **15**, 2005, 285, *An excellent review of pain management in the critical care setting. Includes the addition of nonopioid aspects of pain management to complement opioid-based techniques and emphasizes intravenous and continuous intravenous administration.*

PW Hellyer: Pain management. In WE Wingfield, MR Raffe (Eds.): *The veterinary ICU book*. 2002, Teton New Media, Jackson Hole, WY, *An excellent review of pain management in critical care. Emphasized multimodal or balanced analgesia.*

N Shaffran, K Taylor, A Battaglia: Pain management in critical care: the veterinary nurse/technician's perspective. *J Vet Emerg Crit Care*. **15**, 2005, 240, *Excellent comments on analgesia in veterinary critical care from the perspective of veterinary technicians and their role on the medical team.*

Stein RM: Veterinary Anesthesia & Analgesia Support Group web site http://www.vasg.org, Accessed March 12, 2007 *Excellent resource on many topics in veterinary anesthesia and analgesia.*

* See the CD-ROM for a complete list of references

185 Chapter 185 Benzodiazepines

Ralph C. Harvey, DVM, MS, DACVA

185.1 KEY POINTS

- Benzodiazepines are associated with less adverse respiratory and cardiovascular effects than most alternative tranquilizers or sedatives.
- Benzodiazepines are a first line of defense for seizure control.
- Short-term appetite stimulation in critically ill cats is often successful with small doses of benzodiazepines.
- Accidental ingestion of benzodiazepines is treated with supportive care, emetics or activated charcoal, or both, and flumazenil may be administered in severe cases with marked central nervous system depression.

185.2 INTRODUCTION

Benzodiazepines have a wide range of applications in critically ill patients. As a group these drugs offer effects that include sedation, anxiolysis, and anticonvulsant activity, with minor cardiovascular and respiratory effects. They can be used as part of an anesthetic induction protocol for balanced anesthesia, with analgesic drugs to enhance patient comfort and sedation, as well as treatment of status epilepticus. The most commonly used benzodiazepine in veterinary medicine is diazepam, although midazolam appears to be growing in popularity. Benzodiazepines are considered controlled substances in the United States (C-IV) and, as such, require appropriate storage and documentation.[1]

185.3 ACTION

The primary mechanism of action of benzodiazepines is believed to be via the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Benzodiazepines bind to stereo-specific receptors that facilitate the inhibitory actions of GABA.[1,2] The mechanism of action may also involve antagonism of serotonin and diminished release or turnover of acetylcholine in the Central nervous system (CNS).[1] Benzodiazepines act at the limbic, thalamic, and hypothalamic level of the CNS with anxiolytic, sedative, hypnotic, skeletal muscle relaxant, and anticonvulsant properties. In humans, benzodiazepines are also recognized to have anterograde amnestic effects, providing amnesia for events that occur subsequent to the administration of the drug.[2] Benzodiazepines are generally considered to provide no analgesia.

Benzodiazepines are metabolized in the liver to active metabolites that, after conjugation, are excreted in the urine.[2]

185.4 DIAZEPAM VERSUS MIDAZOLAM

Diazepam and midazolam have similar pharmacologic actions in dogs and cats. The major difference between these drugs is that diazepam is not water soluble and is formulated in a 40% propylene glycol and 10% alcohol vehicle.[1] Propylene glycol is an irritant to blood vessels and will cause phlebitis and thrombosis after repeated or continuous administration in a peripheral vein. For this reason diazepam should be given only as a constant rate infusion (CRI) or multiple repeated intermittent doses via a central vein. Prolonged administration of diazepam can also cause propylene glycol toxicity, which can have life-threatening effects including metabolic acidosis, hyperosmolality, neurologic sequelae, and organ dysfunction.[3] Propylene glycol toxicity is of particular concern in cats, so diazepam infusions are not recommended in this species.[4] Diazepam will also adsorb to plastic, so doses should not be stored in plastic syringes for any length of time, and infusion lines may require precoating with the drug before administration. Both diazepam and midazolam should be protected from light.

In contrast to diazepam, midazolam is water soluble and is well absorbed after intramuscular injection but is poorly bioavailable when given per rectum to dogs, so this route of administration is not recommended.[1] Diazepam rectal gel is available for human use and may offer a viable alternative for at-home treatment of seizures using rectal diazepam. Midazolam can be given as a CRI through a peripheral vein.

185.5 BENZODIAZEPINES AND CATS

The sedative effects of benzodiazepines are highly variable in dogs and cats. They may demonstrate aberrant behavior after benzodiazepine administration including excitation, irritability, and depression. Patients that are already somewhat obtunded are likely to be effectively sedated, particularly if the benzodiazepine is combined with an opioid. Healthier dogs and cats may demonstrate dysphoria; this is more likely when the drugs are used as sole agents.

A rare complication of oral diazepam in cats is fulminant hepatic failure. This has been reported as an idiosyncratic reaction resulting in acute hepatic necrosis.[5] This has not been reported in association with other routes of administration.

185.6 INDICATIONS

185.6.1 Sedation

As a sole drug a benzodiazepine is rarely sufficient to sedate neurologically normal dogs and cats. Benzodiazepines commonly are combined with opioids to provide sedation for intensive care procedures, or to relieve distress and anxiety in critically ill patients when analgesic therapy alone is insufficient.[4] Benzodiazepines are also commonly incorporated in anesthetic protocols for induction and maintenance of anesthesia. These drugs can reduce the required dosage of other anesthetic agents such as propofol or barbiturates in an effort to minimize their adverse effects.

Table 185-1 Suggested Parenteral Dosages for Benzodiazepines in Dogs and Cats

Indication	**Diazepam**	**Midazolam**
Sedation	0.2 to 0.6 mg/kg IV	0.1 to 0.4 mg/kg IV, IM
	CRI: 0.1 to 1 mg/kg/hr (central vein)	*CRI:* 0.1 to 0.5 mg/kg/hr
Anticonvulsant	0.5 to 1 mg/kg IV or intranasally Can repeat 2 to 3 times	0.2 to 0.5 mg/kg IV, IM Can repeat 2 to 3 times
	PR: 2 mg/kg	*CRI:* 0.2 to 0.5 mg/kg/hr
	CRI: 0.5 to 1 mg/kg/hr (central vein)	

CRI, Constant rate infusion; *IM,* intramuscular; *IV,* intravenous; *PR,* per rectum.

The shorter acting midazolam is often given intravenously and is preferred to diazepam. It can be titrated easily to a desired level, preventing drug accumulation that would delay recovery. Water-soluble midazolam may be more suitable for continuous infusion than diazepam. The pharmacologic properties of water solubility, short duration of action, and short elimination half-life are desirable characteristics in critical care applications when titration to desired and sustained effects are desired. The more slowly eliminated benzodiazepine, lorazepam, is also water soluble and has been recommended as an alternative and more suitable for longer term use in human patients, but there is little experience with this drug in veterinary patients.[4,6]

The most important adverse effects of long-term benzodiazepine infusion are dysphoric or excitatory signs and, occasionally, delayed awakening. The antagonist flumazenil and the inverse agonist sarmazenil have each been used to reverse CNS depression or dysphoria due to benzodiazepine agonists in human patients. Significantly delayed recovery or marked dysphoria attributable to benzodiazepines may be responsive to reversal with these agents, but neither can be recommended for routine use. Marked excitement and dysphoria can be precipitated by either drug. Significant adverse effects, such as seizures and acute benzodiazepine withdrawal, have been reported.

In most cases, the delayed recovery or adverse effects of the benzodiazepines are less problematic than the potential for more severe adverse outcomes resulting from either flumazenil or sarmazenil. Even in cases of severe benzodiazepine overdose, as from oral ingestion of multiple tablets, the toxic effects are generally managed with supportive care, emetics, or activated charcoal. Benzodiazepine antagonist therapy with flumazenil is rarely indicated.[7] When flumazenil therapy is deemed necessary, a dosage of 0.01 to 0.02 mg/kg IV has been recommended for reversal of benzodiazepine effects in dogs and cats.

185.6.2 Anticonvulsant Therapy

Benzodiazepines are the drugs of choice for initial control of status epilepticus in both dogs and cats.[9,10] Midazolam can be given intramuscularly if intravenous access is not available. It is not recommended to administer diazepam IM, and the rectal or intranasal route is preferred in the absence of IV access.[1,11,12] Diazepam rectal gel (Diastat) is available, however, for rectal administration in animals having seizures, at home or in the hospital before intravenous access is obtained. It has not been extensively studied in small animals, but is expected to act similarly to diazepam given by other routes. For patients with recurrent seizure activity, that responds to benzodiazepine therapy a CRI of diazepam or midazolam may be effective. See Table 185-1 for some suggested anticonvulsant doses. Chapter 98 and 186, Seizures and Status Epilepticus and Anticonvulsants, respectively, discuss anticonvulsant therapy and the approach to the seizing patient in detail.

185.6.3 Appetite Stimulation

Low doses of benzodiazepines can stimulate appetite in many species, especially in cats. The hyperphagic effect is separate from sedation or anxiolysis, involves binding to benzodiazepine receptors, and appears to increase the attraction to tastes. Increases in both the amount of food consumed and rate of consumption are noted. In experimental models, the hyperphagic response is seen in satiated (fully fed) animals. As an appetite stimulant, diazepam is administered to cats at 0.05 to 0.4 mg/kg, IV q 24h, or 1 mg PO (risk of hepatic toxicity should be considered). Food should be readily available, because the animal may begin eating within a few seconds.[1]

185.7 HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (HE) commonly accompanies the syndrome of portosystemic shunting or other causes of significant hepatic insufficiency (see Chapters 103 and 127, Hepatic Encephalopathy and Hepatic Failure, respectively). Human patients with HE have occasionally shown arousal on administration of the benzodiazepine antagonist flumazenil. This observation suggested that the syndrome may involve increased endogenous benzodiazepine agonist activity. In contrast, a lack of arousal in other species, including dogs and cats in both clinical and research models of HE, has been interpreted as evidence that endogenous benzodiazepines are not increased in this syndrome.

Administration of the benzodiazepine inverse agonist sarmazenil, but not the antagonist flumazenil, in animal research models of both acute and chronic HE has resulted in improvement of encephalopathic signs. This is consistent with an increased GABAergic constitutive activity in HE, rather than an increase in endogenous benzodiazepine agonist ligands.[13] Although sarmazenil has been useful in elucidating the pathophysiology of HE, 791 it should not be considered part of the therapeutic modality for this disorder. Sarmazenil has also been used for 792 reversal of GABA-mediated toxicity due to moxidectin in a foal.[14] As with the effectiveness of benzodiazepines for the treatment of seizures in the patient with HE, this application remains somewhat controversial at this time.

185.8 SUGGESTED FURTHER READING*

BD Hansen: Analgesia and sedation in the critically ill. *J Vet Emerg Crit Care*. **15**, 2005, 285, *An excellent review of sedation and analgesia in the critical care setting*.

J Parent, R Poma: Single seizure, cluster seizures, and status epilepticus. In WE Wingfield, MR Raffe (Eds.): *The veterinary ICU book*. 2002, Teton NewMedia, Jackson Hole, WY, *Another excellent review of seizure management*.

DC Plumb: Diazepam. In DC Plumb (Ed.): *Plumb's veterinary drug handbook*. ed 5, 2005, Blackwell, Ames, IA, *The essential veterinary drug formulary*.

* See the CD-ROM for a complete list of references

186 Chapter 186 Anticonvulsants

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186.1 KEY POINTS

- The first-line drug for control of status epilepticus is diazepam. In animals refractory to this drug, a midazolam or propofol bolus and infusion are administered.
- Oral phenobarbital (PB), the first-line antiepileptic drug (AED) for chronic seizure control in dogs and cats, is typically titrated to clinical effect and therapeutic serum levels (20 to 40 μg/ml in dogs; 10 to 20 μg/ml in cats).
- PB administration induces hepatic microsomal enzymes and may lead to drug-drug interactions.
- Potassium bromide is an effective second-line AED in dogs and cats, although its use is limited in cats because of the risk of inducing severe lower airway disease in this species.
- In contrast to its effect in dogs, oral diazepam is effective for long-term control of seizures in cats. However, the risk for liver failure after oral, but not intravenous, administration restricts its use in cats.
- Newer AEDs exert pharmacokinetic properties associated with little or no drug-drug interaction. Limited clinical data suggest potential benefit as add-ons or monotherapy in small animals.
- The most common side effects of antiepileptic therapy include sedation and ataxia. Abrupt withdrawal of any of the short-acting AEDs can induce seizure activity.

186.2 INTRODUCTION

The emergency and critical care veterinarian often is presented with small animal patients that have:

- *New-onset seizures*
- *Cluster seizures:* multiple seizures in a 24-hour period
- *Status epilepticus:* a continuous, generalized, convulsive seizure lasting more than 5 minutes, or two or more seizures between which no normalization of mental status occurs
- *Refractory status epilepticus:* seizures lasting more than 2 hours or more than two seizures per hour without normalization of mental status, despite standard antiepileptic treatment[1] (see Chapter 98, Seizures and Status Epilepticus)

Although antiepileptic drugs (AEDs) are an essential, although not solitary, part of patient management in all of the above scenarios, the side effects of these medications may be responsible for considerable morbidity that necessitates a high level of medical care. Furthermore, the pharmacokinetic behavior of many AEDs is influenced not only by concurrently administered medications and vice versa, but also by dysfunction of the organs most involved in their elimination, such as the liver and kidneys. To consider the pharmacologic characteristics of AEDs in the assessment and management of critically ill patients is thus of particular importance.

186.3 PHENOBARBITAL

Phenobarbital (PB) is a long-acting barbiturate that exerts its anticonvulsive effects by enhancing the postsynaptic effect of the major inhibitory neurotransmitter γ-aminobutyric acid (GABA) on the GABA_A receptor, thus leading to increased influx of chloride anions into the cytoplasm. This leads to hyperpolarization of the postsynaptic membrane (i.e., a more negative resting membrane potential). Furthermore, PB inhibits the activity of the excitatory neurotransmitter glutamate and limits calcium passage across the neuronal membrane.[2] The net result of the above mechanisms is an increase in the seizure threshold, along with a reduction in the spread of a focal discharge to surrounding areas. The drug's multiple mechanisms of action make it an effective anticonvulsive medication for most types of epileptic seizures.

PB is a weak acid (pKa 7.3) with high oral bioavailability, despite a relatively slow increase in plasma concentration (which peaks after 4 to 8 hours).[2] Approximately 50% of the drug is bound to plasma proteins.[3] Up to 25% of PB is eliminated unchanged by renal excretion, a mechanism that is pH dependent; alkaline urine accelerates excretion by increasing the ionized fraction of the drug.[2] Most of the drug is inactivated by hepatic microsomal enzymes (P-450 enzymes), some of which are induced by PB, thereby leading to a shorter elimination half-life (by 50% after 90 days).[2]

Generally PB is well tolerated by dogs at therapeutic levels (20 to 40 μg/ml).[4] Fast development of tolerance leads to disappearance of initial behavioral abnormalities like sedation, fatigue, restlessness, or hyperexcitability that commonly occur within the first 7 days of administration.[4] Long-term administration of PB has been associated with hepatic injury, which is more likely to occur with high plasma levels (above 35 μg/ml).[5] Animals that were euthanized because of liver failure secondary to long-term PB administration were found to have hepatic cirrhosis on necroscopic histopathologic examination. There is evidence that alkaline phosphatase and alanine transaminase can be elevated as a result of enzyme induction in dogs treated with PB,[6] although this has been questioned.[7] The clinician must determine whether elevations of these enzymes in clinically normal dogs is due to enzyme induction or to subclinical hepatocellular damage.

In contrast, alterations in serum aspartate transaminase, fasting and postprandial bile acid levels, total bilirubin values, and the ultrasonic appearance of the liver may be more helpful to confirm hepatic disease.[6] Microsomal enzyme induction associated with PB therapy decreases serum free and total thyroxin but not triiodothyronine concentrations and may increase thyroid-stimulating hormone.[8-10] There is no apparent influence on adrenal axis function (e.g., adrenocorticotropic hormone stimulation test).[4] A potentially life-threatening idiosyncratic reaction to PB in the form of neutropenia, thrombocytopenia, and anemia is described in the literature.[11] Superficial necrolytic dermatitis was reported in 11 dogs after long-term treatment with PB.[12] These side effects warrant vigilant monitoring of biochemical, hematologic, and clinical parameters every 6 months during long-term treatment.

Oral PB therapy is started at a dosage of 2.5 mg/kg q12h. Because of the long elimination half-life, steady state concentrations will be reached after 2 weeks, when the first serum PB level should be measured. Trough levels of 20 to 25 μg/ml are the initial therapeutic target. Trough serum levels should be determined 2 weeks after each dosage adjustment, when considered clinically effective, and after 45, 90, 180, and 360 days and twice a year thereafter in a consistent manner (e.g., before administration). This is essential because serum PB levels can vary considerably among dogs receiving an identical oral dose.[13] A sudden drop in plasma PB levels can induce withdrawal seizures, so a loading dose of another AED, such as potassium bromide, should be administered concurrently to prevent this.

In patients that are already receiving PB, adjustments are made to reach a clinically effective dosage that can vary widely among animals:

$$\begin{aligned}&(\text{Desired concentration} \div \text{Actual concentration})\\&\quad\times \text{Actual total mg PB per day}\\&\quad= \text{Oral daily dosage of PB (mg)}\end{aligned}$$

Animals with severe or refractory seizures may benefit from rapid intravenous loading with a total of 12 to 20 mg/kg as a slow bolus or divided and administered q4-6h over 24 hours to achieve a serum concentration of 20 to 40 μg/ml. More pronounced sedation, hypotension, and hypoventilation should be anticipated in patients treated with this regimen.

PB is also the recommended first-line AED in cats. When compared with use in dogs, the elimination half-life is longer and does not change over time.[14] An initial administration of 1 to 2 mg/kg PO q24h can be altered to 1 to 3 mg/kg q12h as needed, according to clinical effect and serum levels; 3 mg/kg q12h is often necessary. The target concentration in cats is 10 to 20 μg/ml.[4] This is important, because drug elimination and therefore serum concentrations appear to vary among feline populations.[14] Polyphagia, polydipsia, and polyuria frequently accompany PB administration in the cat, and sedation can be problematic at higher dosages. Hepatotoxicity has not been reported as a complication in cats.

In animals with renal failure, a reduction in the PB dosage may be necessary, although the contrary is true during peritoneal dialysis or hemodialysis, as directed by serum trough levels after a dialysis treatment. Low albumin levels, a frequently occurring abnormality in the critically ill patient, will increase the free serum PB concentration, and a decrease in dosage may be required.

Because of the significant and broad-spectrum hepatic enzyme–inducer properties of PB, drug-drug interactions have to be expected.[15,16] Although this is important in the intensive care setting in which patients receive a large number of medications, reports for the relevance of individual interactions are scarce in the veterinary literature.

186.4

PHENYTOIN

The hydantoin derivative phenytoin (diphenylhydantoin) is very effective against all types of seizures. Its mechanism of action is distinctively different from that of PB in that it arrests voltage-activated sodium channels in their inactivated, closed conformation.[3] Bioavailability of the oral formulation is only around 40% in the dog, and it is highly bound to plasma proteins.[2] In this species, phenytoin potently induces hepatic microsomal enzymes, shortening not only the effect of other AEDs like PB, but also reducing its own elimination half-life by 75% after 9 days.[17,18] This, along with the low bioavailability, makes it difficult to achieve and maintain effective plasma levels with the oral formulation in dogs. However, phenytoin is available for intravenous injection and can be used for termination of status epilepticus, but this often causes marked hypotension in dogs. Hepatotoxicity is a major side effect of phenytoin, especially when administered in combination with primidone or PB. In contrast to that in dogs, the phenytoin elimination half-life in cats is very long. The risk for accumulation with subsequent intoxication appears to be high and its use in this species is therefore not recommended.

186.5 BROMIDE

Potassium bromide (KBr) frequently is used either as an add-on AED in dogs with seizures refractory to PB or for monotherapy, especially in cases with PB-associated hepatotoxicity. Although its precise mechanism of action is unknown, its preferential movement through GABA-activated chloride channels may lead to hyperpolarization of neuronal cell membranes.[2] Oral bioavailability is 47% in dogs receiving KBr solution.[19]

Bromide is only minimally bound to plasma protein and is eliminated unchanged by renal excretion. Characteristically, bromide has a very long elimination half-life in dogs (varying from 15 to 69 days).[20,21] Because approximately 5 times the elimination half-life must elapse until steady-state conditions exist, this may take up to 4 to 5 months in dogs. On the flip side, the long half-life of the drug prevents a significant impact on serum drug concentrations when several days of administration are missed. An increase in chloride intake accelerates bromide elimination by reducing its renal tubular reabsorption, and this mechanism is considered the major contributor to the wide variability in the bromide elimination half-life.[20] For this reason, variations in dietary chloride intake may significantly change bromide plasma concentrations. Intravenous sodium chloride administration can be used to treat animals with bromide intoxication.

Generally KBr is well tolerated in dogs. Orally administered bromide can lead to gastric irritation, especially with use of capsules that localize a high concentration in a small area of gastric mucosa. In contrast to PB, hepatotoxicity is not a concern with administration of KBr, but pancreatitis has been reported when used in combination with PB in dogs.[22] Signs of neurotoxicity (bromism) can occur at serum bromide concentrations within the target range (1.5 to 3 mg/ml), but they are seen more commonly when concentrations reach higher levels.[4] Signs consist of ataxia, progressive quadriplegia with normal reflexes, and hind limb weakness, stiffness, or swelling. Lethargy and sedation, progressing to stupor and coma, have also been described.[23,24]

If intravenous sodium chloride administration is considered for the treatment of bromism, caution should be used because the fast drop of the bromide concentration could trigger recurrence of seizures.[24] Some precautions should also be considered in animals with comorbidities. Renal failure likely reduces bromide clearance, and dosage adjustments according to bromide serum concentrations are needed to avoid bromism.[24] In animals with diseases affecting potassium regulation, such as hypoadrenocorticism, KBr should be used carefully and sodium bromide (NaBr) should be considered to prevent worsening a hyperkalemic state. Animals with congestive heart failure or hypertension might not tolerate the amount of sodium associated with NaBr management, especially when used for initial loading. Serum chloride concentration may be falsely elevated because some laboratory equipment does not distinguish between bromide and chloride.

A serum bromide concentration of 0.8 to 3 mg/ml is targeted for treatment of seizures in dogs, depending on the level of seizure control achieved and whether KBr is used as monotherapy or in combination with PB.[2,4,25] An oral KBr dosage of 15 to 30 mg/kg/day as an add-on drug and 30 to 50 mg/kg/day as monotherapy is usually sufficient. Serum bromide concentrations should be determined after 1 and 3 months of treatment. To reach effective serum concentrations more rapidly, a loading dose of KBr (400 to 600 mg/kg) can be divided into 4 equal doses over 24 to 48 hours. This will lead to a serum bromide concentration of 1 to 1.5 mg/ml quickly, but can cause significant gastric irritation. Also, this protocol is not applicable to animals unable to tolerate oral nutrition, as is frequently the case in the intensive care setting.

Rectal bioavailability of bromide is close to 100%, and loading by this route should be considered in patients with refractory status epilepticus. The loading dose of KBr or NaBr can be administered rectally divided in 4 equal doses distributed over a 24-hour period.[26] The solution should be diluted to prevent colitis.

Potassium and sodium bromide have different molecular weights: KBr and NaBr contain 67% and 77% bromide, respectively, per unit weight, and it is recommended to decrease the dosage by 15% to account for the higher bromide content of the sodium salt.[27] Alternatively, NaBr can be administered intravenously. A loading dose of 600 to 1200 mg/kg NaBr given by continuous infusion over q8-24h hours will result in a median peak serum bromide concentration of 2.5 mg/ml.[19,28]

KBr has been effective in the control of seizures in cats, although to a lesser extent than in dogs. Administration of 15 to 25 mg/kg KBr resulted in serum bromide levels of 1 to 1.6 mg/ml, which was sufficient to control seizures in 7 out of 15 cats evaluated in one study.[29] One third of the cats developed asthma-like respiratory tract changes, however, manifesting as a nonproductive cough and leading to euthanasia of one of the cats.[29] This is supported by additional reports in the literature.[30,31] Routine administration of KBr in cats for treatment of seizures can therefore not be recommended.

186.6 BENZODIAZEPINES

Benzodiazepines (BZs) are the first-line AEDs for termination of status epilepticus in both dogs and cats. Similar in action to the barbiturates, BZs act on the $GABA_A$ receptor, although at a different binding site. By doing so, BZs enhance chloride influx and hyperpolarize the postsynaptic membrane.

Diazepam is the most extensively used BZ for acute control of seizure activity in veterinary patients. It is well absorbed after oral administration; however, its short elimination half-life of around 3 hours and the fast development of tolerance make it unsuitable for long-term antiepileptic therapy.[2] Its high lipid solubility leads to fast passage across the blood-brain barrier and quick termination of seizures. Diazepam, like all of the BZs, causes only mild cardiorespiratory depression; however, it will exacerbate hemodynamic and respiratory compromise secondary to other medications or preexisting illnesses.

Sedation usually occurs, but a paradoxical response with excitement, pacing, disorientation, and vocalizing may also occur. An intravenous bolus of 0.25 to 0.5 mg/kg is administered for termination of status epilepticus and can be repeated if required. Initiation of a constant rate infusion (CRI) of 0.2 to 1 mg/kg/hr can be attempted in dogs with uncontrolled seizures until other measures, such as loading with either PB or bromide, become effective.

Diazepam is a vascular irritant, and thrombophlebitis will occur unless it is infused into a large vessel, such as through a central venous catheter. Large amounts of diazepam (40% or more) adsorb to plastic tubing initially, which necessitates an increase in dosage during the first few hours. The dosage can be decreased once the tubing has been saturated and is generally titrated to effect.[32]

Diazepam solutions contain propylene glycol in the amount of 40% (400 mg/ml), which has been implicated in hemolysis, lactic acidosis, hypotension, hyperosmolarity, cardiac arrhythmias, seizures, and coma in humans sedated long term with the drug.[33]

Using midazolam instead of diazepam may alleviate the issue because midazolam is formulated in a propylene glycol–free solution, although this has not been evaluated systematically in dogs. Furthermore, midazolam is

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preferable over diazepam for prolonged CRI administration because of its other properties, such as shorter elimination half-time, less accumulation, lack of venous irritation, and absence of adsorption to plastic tubing.

Intraosseous administration of diazepam will lead to serum concentrations comparable to those of the intravenous route and is tolerated well. Owner administration at home of the injectable solution of diazepam rectally (0.5 to 1 mg/kg) to dogs experiencing generalized cluster seizures was effective in reducing the total number of seizures and cluster seizures (and thus emergency room visits).[34] Diazepam rectal gel (Diastat) is available, however, for rectal administration in animals having seizures, at home or in the hospital before intravenous access is obtained. It has not been extensively studied in small animals, but is expected to act similarly to diazepam given by other routes. The pharmacokinetics of intranasally instilled diazepam have been determined in dogs, and this route of administration may prove to be effective for seizure control.[35] However, great caution should be exerted to prevent being bitten by the convulsing animal when this route of administration is used.

Diazepam is a suitable medication for long-term antiepileptic treatment in cats because of its longer elimination half-life (20 hours), lack of tolerance, and good efficacy. The recommended dosage range is 0.5 to 2 mg/kg PO q24h, divided q8-12h starting with the lower end of the dosage to prevent excessive sedation.[4] Rare cases of idiosyncratic acute hepatic necrosis have been documented with oral diazepam administration in cats,[38] and the benefits should be weighed carefully against the risks before prescribing this medication. Whether other BZs such as clonazepam or clorazepate, both of which have been used successfully for treatment of seizures in cats,[4] are devoid of this adverse reaction remains to be shown. Liver enzymes should be evaluated within the first week and the first month of treatment, and every 6 to 12 months thereafter. Elevation of liver enzymes should prompt discontinuation of the drug.

Clorazepate has been used in dogs.[2] Clorazepate is a prodrug that is metabolized to its active metabolite nordiazepam (desmethyldiazepam) in the gastrointestinal tract, where it is absorbed almost completely. Clorazepate can be used as an oral long-term AED because tolerance is lower than that associated with diazepam and other BZ drugs. Clorazepate was shown experimentally to be effective in increasing the seizure threshold[35] and is successfully used as an add-on drug at a dosage of 2 to 4 mg/kg q24h, divided q12h in dogs with seizures.[4] Concurrent administration of PB decreases serum nordiazepam levels, and the dosage may have to be adjusted accordingly.[36] Sudden discontinuation of clorazepate carries a risk of withdrawal seizures.[37]

Lorazepam, an injectable BZ in propylene glycol solution, has been well evaluated for rapid termination of status epilepticus in humans and is considered equally or more effective than diazepam for this indication.[39,40] Pharmacokinetic data for lorazepam after intravenous and rectal administration to dogs are available, but a systematic evaluation of its antiepileptic efficacy in veterinary species is lacking.[41]

186.7 NEWER AGENTS

186.7.1 Levetiracetam

Levetiracetam is a newer AED that has a promising pharmacologic profile: it is absorbed almost completely after oral administration, it is not bound to plasma proteins, its metabolism is independent of the hepatic cytochrome P-450 system, it is excreted largely unchanged by the kidneys, and it is very well tolerated.[4,42-44] Although its mechanism of action remains unknown, it was effective for add-on therapy in humans with refractory seizures, and in 15 dogs it reduced the incidence of seizures that were poorly controlled with PB and KBr by more than

50%.[44] It does not appear to influence PB or KBr serum levels, and its pharmacokinetic profile is not altered by other AEDs.

Coadministration of levetiracetam allowed PB dosage reduction in dogs with barbiturate-induced clinical hepatopathy without increasing the seizure frequency.[43] A wide dosage range of 5 to 30 mg/kg q8-12h has been recommended in dogs, and 10 to 20 mg/kg PO q12h has been used successfully in cats.[4,45] Very limited data are available about the efficacy and safety of levetiracetam in cats. However the anecdotal information suggests that the drug is well tolerated by dogs and cats and that side effects consist predominantly of sedation during the first week of treatment.[45]

186.7.2 Zonisamide

Zonisamide, a sulfonamide-based substance, exerts its antiepileptic effects by blocking T-type calcium channels and voltage-gated sodium channels, thereby stabilizing neuronal membranes.[3] Pharmacokinetic data available for dogs suggest that the drug is well absorbed after oral administration and has a comparatively long elimination half-life of approximately 15 hours.[4] In humans it is highly protein bound and, as a sulfonamide, has a high affinity for red blood cells, in which it reaches 8 times the plasma concentration. It is partially metabolized by the liver and most of an oral dosage is excreted renally as the parent substance.[3] Zonisamide does not induce its own metabolism or that of other AEDs; however, its hepatic clearance is enhanced by hepatic enzyme inducers such as PB.[15] High dosages of the drug were well tolerated by dogs in a chronic toxicity trial.[46] In a small prospective study of dogs with poorly controlled idiopathic epilepsy, a dosage of 5 to 10 mg/kg PO q12h as add-on therapy was found to produce serum levels within the therapeutic range described for humans (10 to 40 µg/ml) and to reduce the seizure frequency in 7 of 12 dogs.[47] Mild and transient adverse effects were seen (sedation, ataxia, and vomiting).[47] Zonisamide use in cats with seizures has not been clinically evaluated.

186.7.3 Felbamate

The exact mechanisms by which felbamate, a dicarbamate, exerts its anticonvulsive effects are not fully elucidated and multiple modes of action appear to be involved. Its antagonistic effect on N-methyl-D-aspartate receptors within the central nervous system is considered the most important mechanism of action.[48]

Felbamate's pharmacokinetic profile in dogs has been evaluated.[49] The drug is completely absorbed after oral administration and is approximately 25% bound to plasma proteins. The total plasma clearance of felbamate in dogs is the sum of hepatic clearance due to oxidative metabolism (approximately 75%) and renal clearance of unchanged drug (approximately 25%). Dosage adjustment is recommended in humans with impaired renal function, and the same recommendation should be considered in dogs. One study reported that the elimination half-life in dogs was 4.1 to 4.5 hours.[49]

In humans, felbamate increases the steady-state concentration of PB and phenytoin, and phenytoin, but not PB, increases felbamate clearance. The drug has been used successfully for monotherapy in dogs with partial seizures.[50] Dosing is started at 20 mg/kg PO q8h with target trough serum levels between 25 and 100 µg/ml (determined 1 to 2 weeks into management).[4] Adverse effects collected from clinical and toxicologic studies in dogs are minor at clinically relevant dosages and may include transient liver enzyme increases (alanine transaminase, alkaline phosphatase) and keratoconjunctivitis.[50,51] Its use in humans is limited to people with seizures refractory to other AEDs because of possible idiosyncratic reactions (aplastic anemia and acute liver failure). Abrupt withdrawal can promote seizures.

186.7.4 Gabapentin

Despite its design as a GABA analog, gabapentin has no direct GABAergic effect and its mechanism of action is not fully understood.[2] Its effect may be partially due to facilitation of nonvesicular GABA release.[2] Gabapentin is well absorbed after oral administration. Although it is metabolically inert in people and is excreted renally in its unaltered form, biotransformation to N-methyl-gabapentin is found in dogs.[52] The parent drug and its metabolites are eliminated almost exclusively by the kidneys; a dosage reduction should be considered in animals with renal failure. Elimination half-life is 3 to 4 hours in dogs, which necessitates frequent administration.[52] Gabapentin, along with levetiracetam, causes the fewest AED interactions.[15] It has been used as an add-on AED in dogs with insufficient seizure control with PB or KBr and was found to reduce seizure frequency or prolong the interictal period.[53,54] In addition, gabapentin has been administered as a temporary drug to control cluster seizures. Suggested dosage range is 30 to 60 mg/kg q24h divided q8-12h Because significant sedation may occur initially, low starting dosages are recommended.[4] Besides the central nervous system depressant effect, the drug has very little toxicity and is well tolerated. It is recommended in dogs with seizure disorders and concomitant liver disease.

In cats, the pharmacologic profile of gabapentin is assumed to be similar to that in dogs and its use can be considered in cats with liver disease or portosystemic shunts. It has been used in cats both for monotherapy and as an add-on drug. Because sedation may be more pronounced than in dogs, starting at a low dosage and approaching the target dosage in small increments over 1 to 2 weeks are preferred. An empirically determined dosage is 5 to 10 mg/kg q24h, q12-24h in this species.[4]

186.8 PROPOFOL

Propofol (2,6-di-isopropylphenol) is used extensively as an intravenous anesthetic for both induction and maintenance of general anesthesia in various species. It is also effective in controlling refractory status epilepticus in humans, dogs, and cats, especially those secondary to hepatic encephalopathy.[1,55,56] It exerts its anticonvulsive properties via effects on the $GABA_A$ receptor complex, although at another site and on different ion channels (such as brain sodium and calcium channels) than for the BZs. Propofol is fast acting and highly lipid soluble. It has a short duration of action because of its hepatic and extrahepatic metabolism and large volume of distribution.[57] In humans, the pharmacokinetics of propofol are not altered by hepatic and renal impairment. In the elderly, both pharmacodynamic and pharmacokinetic alterations explain lower dosage requirements, and the same has been documented in dogs.[58] In cats and dogs, dosages of 1 to 4 mg/kg IV bolus and 0.05 to 0.4 mg/kg/min IV as a CRI are used to control seizures. Although the lowest effective dosage should be chosen, significant sedation and cardiovascular and respiratory depression will likely occur, and even more so if given in conjunction with other AEDs. Continuous monitoring of cardiopulmonary performance and providing of appropriate supportive measures are key to prevention of associated morbidity and mortality. In cats, oxidative injury to red blood cells will occur in proportion to dosage and duration and may limit the extent of its use in this species.[59]

186.9 PENTOBARBITAL

Pentobarbital, a short-acting barbiturate, was previously the AED of choice for the treatment of refractory status epilepticus in humans, but it has been largely replaced by midazolam and propofol. This is because its pharmacologic profile is inferior to those of midazolam and propofol: it has a long half-life that causes prolonged sedation after discontinuation, it has highly liver-dependent metabolic degradation, there is a high incidence of withdrawal seizures, it causes hemodynamic instability, and it causes immune paresis.

Although no controlled trials have been undertaken to show benefit in clinical efficacy or outcome by using one drug over another, the general recommendation is to use pentobarbital therapy only after midazolam and propofol have failed to control seizure activity[1]; a similar recommendation may be the most rational in small animals. A suggested dosage is 2 to 15 mg/kg IV bolus (to effect) and can be continued as an IV CRI at 0.1 to 5 mg/kg/hr as needed. Pentobarbital elimination is entirely dependent on hepatic metabolism, and renal failure does not have an influence on its pharmacokinetics, although uremia increases sensitivity to the drug (probably by reduction of the protein-bound fraction).[60]

186.10 INHALATIONAL ANESTHETICS

In humans, inhalational anesthetics are highly effective in controlling refractory status epilepticus by mechanisms that are incompletely understood.[61] Responsiveness to GABAergic AEDs may be diminished with prolonged seizures, so that the end point of seizure control with inhalant anesthetics is to allow time for GABAergic antiepileptic mechanisms to recover and for non-GABA AEDs to reach target serum concentrations. Efficacy, rapid onset of action, and easy titration to effect (e.g., burst suppression on EEG) make inhalational anesthetics attractive AEDs. Isoflurane and desflurane are preferred because of their high degree of metabolic inertness.[61] A maximum of 1 to 4 times the minimum alveolar concentration of isoflurane was necessary to achieve sufficient burst suppression in humans.[61] Almost invariably, measures to control associated side effects include intubation, mechanical ventilation, intravenous fluid loading, and vasopressor administration, along with appropriate nutritional and nursing care, which taken together, render this approach labor and cost intensive.

186.11 SUGGESTED FURTHER READING*

DM Boothe: Anticonvulsant drugs and analeptic agents. In HR Adams (Ed.): *Veterinary pharmacology and therapeutics*. ed 8, 2001, Iowa State University Press, Ames, IA, *Comprehensive review of pharmacologic data for older AEDs in various veterinary species*.

DM Boothe, KL George, P Couch: Disposition and clinical use of bromide in cats. *J Am Vet Med Assoc*. **221**, 2002, 1131, *Prospectively evaluates pharmacokinetics and retrospectively examines clinical effects of bromide therapy in the cat, finding that a large percentage of cats developed respiratory complications, leading to euthanasia of one*.

SA Center, TH Elston, PH Rowland, et al.: Fulminant hepatic failure associated with oral administration of diazepam in 11 cats. *J Am Vet Med Assoc*. **209**, 1996, 618, *Case series describing acute fulminant hepatic necrosis after repeated oral administration of diazepam to cats*.

M Podell: Seizures. In SR Platt, NJ Olby (Eds.): *BSAVA manual of canine and feline neurology*. ed 3, 2004, British Small Animal Veterinary Association, Gloucester, UK, *Concise overview of AEDs for dogs and cats, with a clinical focus*.

* See the CD-ROM for a complete list of references

187 Chapter 187 Anticoagulants

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187.1 Box 187-1 International Normalization Ratio

INR = (Patient's prothrombin time ÷ normal patient average time)^{ISI}

ISI = International sensitivity index. This is specific for each formulation of thromboplastin used in the measurement of prothrombin time and is supplied by the manufacturer.

An INR in the range of 2 to 3 has been recommended in human patients requiring anticoagulation.

187.2 KEY POINTS

- Thromboembolic complications may be a significant contributor to morbidity and mortality in critically ill patients.
- Anticoagulant therapy has its effect by altering only one aspect (blood factors) of the hypercoagulability (Virchow's) triad.
- Anticoagulants affect either platelets or clotting factors.
- There are significant risks associated with anticoagulant therapy, so it should be undertaken with care.
- The choice of anticoagulant employed in a particular patient depends on the nature of the hemostatic disturbance, clinician preference, and the ability to monitor therapy.

187.3 INTRODUCTION

Anticoagulants impair the body's ability to form clots. Pathologic blood clots may be formed at the site of a vascular injury, which is termed a *thrombus,* or may be formed elsewhere in the body (such as within the large leg veins) and detach and lodge in a distal location. Movement of a thrombus is termed an *embolic event*. The term *thromboembolism* is used to encompass either type of clot. Clots may also form in the venous or the arterial circulation and in the portal vein. Clinical signs associated with clot formation vary from absent or mild to acutely devastating. The resultant clinical picture may be of severe cardiovascular collapse, which is associated most commonly with massive pulmonary thromboembolism (PTE) or portal vein thrombosis with subsequent severe portal hypertension.

Thromboembolic complications are being recognized increasingly as an important contributor to patient morbidity and mortality in critically ill veterinary patients.[1-3] Prevention of clot formation is therefore warranted for a wide variety of reasons, including cardiac disease, immune-mediated disease, protein-losing conditions, sepsis, and disseminated intravascular coagulation. The most appropriate dosage and appropriate anticoagulant for each condition and species has not been established in veterinary medicine but may depend on several factors such as the nature of hemostatic disturbance (arterial versus venous thrombosis), clinician preference, familiarity with the agents, and ability to monitor therapy. The goals of this chapter are to provide a review of the various anticoagulants and to describe their use in animals.

The normal procoagulant and anticoagulant systems act in balance to provide appropriate hemostasis associated with vascular injury and to limit excessive thrombosis that may be associated with decreased tissue perfusion or other end-organ damage. A hypercoagulable state develops when there are alterations in one or more of the following: blood characteristics (e.g., true hypercoagulability), vascular stasis, and endothelial damage or disruption. The relationship of these three components and thrombus formation is referred to as *Virchow's triad*. In most critically ill animals, abnormalities likely exist in two or even all three of the components of Virchow's triad. An important distinction is that arterial thrombi tend to be composed primarily of platelets and are formed in areas of rapid blood flow. In venous thrombosis, the clot tends to be composed of fibrin and red blood cells and usually is formed in areas of venous stasis or in patients with antithrombin (AT) deficiency.

In people, deep vein thrombosis and PTE are major manifestations of thromboembolic disease. In cats, the most common thromboembolic problem is aortic thromboembolism associated with cardiac disease. Thromboembolic conditions described in dogs include aortic thromboembolism, PTE, and portal vein thrombosis. To date, deep vein thrombosis has not been described in veterinary patients.

In light of differences in the pathogenesis of thrombi, anticoagulant strategies include altering platelet function or affecting clotting factor activity. For ease of classification, anticoagulant medications are commonly divided into (1) antiplatelet drugs, (2) oral anticoagulants, and (3) parenteral anticoagulants. Recommended dosages of these agents are listed in Table 187-1.

Table 187-1 Anticoagulants Used in Veterinary Medicine

Drug	Class Affected	Mechanism of Action	Dosage	Potential Indications	Comments
Aspirin	Platelet	Inhibit TXA_2	0.5 to 2 mg/kg (B)	Feline cardiomyopathy Glomerulonephritis	Inexpensive Readily available Gastrointestinal irritation possible
Clopidogrel	Platelet	Inhibit binding of ADP	18.75 mg total (C) 5 mg/kg (D)	UndeterminedCardiomyopathyGlomerulonephritis	Limited clinical experience
Warfarin	Factors	Inhibit vitamin K–dependent factors	0.1 to 0.2 mg/kg q24h (B)	Marked prothrombotic state	High risk of hemorrhageFrequent rechecks warranted
Unfractionated heparin	Factors	Activates AT Inhibition of II, IX, X, XI, XII	Variable 10 to 25 IU/kg/hr as CRI 25 to 300 IU/kg SC q6-8 h	Hypercoagulable statesSepsisDICThrombotic event	Hemorrhage possibleMonitor aPTTTitrate therapy
LMWH	Factors	Activates ATPreferential inhibition of X over II	Variable 100 to 150 U/kg SC q12-24 h (dalteparin)	CardiomyopathyLong-term home anticoagulation	Product differencesMonitor anti-Xa activity

aPTT, Activated partial thromboplastin time; *AT,* antithrombin; *B,* both; *C,* cats; *CRI,* constant rate infusion; *D,* dogs; *DIC,* disseminated intravascular coagulation; *LMWH,*low-molecular-weight heparin; *TXA,*thromboxane.

187.4 ANTIPLATELET DRUGS

Platelet aggregation at the site of endothelial damage or areas of blood stasis is often the first step in the development of a thrombus. Platelets initially adhere to the site of injury by reacting with exposed submembrane collagen and microfibrils on the damaged wall. Platelet adherence to the damaged endothelium is mediated by collagen and von Willebrand factor and results in the activation of the platelets. Activated platelets then change their discoid shape, becoming small spheres with many projections called *pseudopods*. Platelets stick to one another and form aggregates. This aggregation is mediated primarily by von Willebrand factor and fibrinogen. Certain substances further initiate and maintain platelet aggregation and activation. These substances include the exposed collagen fibers, adenosine diphosphate, serotonin, thrombin, and arachidonic acid metabolites (e.g., thromboxane A_2).[4] Antiplatelet drugs include aspirin, thienopyridine derivatives, and glycoprotein IIb/IIIa antagonists.

187.4.1 Aspirin

Aspirin is the most widely known and used antiplatelet drug. Aspirin acts to permanently inhibit cyclooxygenase (COX) which, in turn, inhibits the synthesis of thromboxane A_2. Thus aspirin is a potent inhibitor of platelet aggregation in response to arachidonic acid, but much less so when stimulated by thrombin. Aspirin is most effective as an antithrombotic agent when administered in low dosages (0.5 to 2 mg/kg q24h) rather than at higher dosages.[5] At high dosages, aspirin will also inhibit the production of prostacyclin and increase the likelihood of clinically significant gastrointestinal ulceration. Additionally, higher dosages may actually result in a hypercoagulable state in dogs.[6] In humans it has also been recognized that some individuals may become "aspirin resistant," which is inconsistently defined but reflects a failure to develop platelet inhibition at the standard dosages.[7] Aspirin resistance may be induced by the co-administration of aspirin with other nonsteroidal antiinflammatory agents (e.g., ibuprofen). This acquired aspirin resistance has not been observed in patients treated concurrently with COX-2–specific agents.[8]

In vitro and in vivo studies have confirmed that aspirin is effective at inhibiting platelet function in dogs when used in low dosages.[8-10] One randomized control trial evaluating dogs with glomerulonephritis treated all dogs with low-dose aspirin, leading some nephrologists to consider low-dose aspirin therapy to be a standard of care for affected dogs.[11] Another retrospective study of dogs with immune-mediated hemolytic anemia included the addition of low-dose aspirin to the standard immunosuppressive therapy, and this report suggested increased short-term and long-term survival in these dogs compared with those that received conventional therapy.[12] Neither of these studies specifically evaluated the effects or benefits of aspirin in these disease processes. The optimal use and dosage of aspirin as an antiplatelet drug in dogs remains to be determined. However, in low dosages, it is a safe, readily available, and inexpensive drug and should likely be considered if antiplatelet activity is deemed necessary.

As an analgesic, aspirin has been used widely in dogs at a dosage of 25 mg/kg PO q12h. At this dosage however, aspirin will decrease the total thyroxine level and may lead to severe gastrointestinal hemorrhage in some dogs.[13,14] It is important to realize that the effects of aspirin therapy may be dosage specific, such that at analgesic levels the drug may lose its antiplatelet properties.

Aspirin has also been used in cats with cardiomyopathy judged to be at high risk of thromboembolic disease at the relatively high dosage of 81 mg/cat 3 times a week. Studies have established that aspirin at higher dosages is effective at inhibiting some stimuli to platelet activation in vitro.[15,16] However, as long as 15 years ago, the rationale of treating all cats with aspirin to prevent thromboembolic disease was being questioned because of lack of efficacy and the potential for side effects.[17] More recently, a single retrospective study advocated low-dose (5 mg/cat q72 h) aspirin as a long-term approach to preventing recurrence of arterial thromboembolism in cats with a prior episode.[18] Thus, in cats, although aspirin effectively alters platelet function, actual clinical efficacy in preventing the devastating complication of arterial thromboembolism is lacking. Further controlled prospective studies are warranted to demonstrate protective benefits associated with aspirin therapy. Nevertheless, a low-dosage approach to aspirin therapy is at the very least unlikely to be harmful in cats affected with cardiomyopathy.

187.4.2 Thienopyridine Derivatives

The thienopyridine derivatives, including ticlopidine and clopidogrel, are another class of antiplatelet drugs that inhibit the binding of adenosine diphosphate to the platelet receptor. These drugs were developed in an attempt to minimize some of the side effects associated with aspirin therapy in humans and to try to provide an effective form of antiplatelet therapy for those patients with aspirin resistance. Clopidogrel (Plavix) and ticlopidine (Ticlid) have been evaluated extensively in humans.[19] Ticlopidine has been associated with more side effects, and thus has been largely replaced by clopidogrel in humans. Clopidogrel is used most widely in patients with cardiovascular diseases (cardiac and peripheral arterial disease). Many cardiologists advocate combining aspirin and clopidogrel in patients at risk for embolic events because their mechanisms of action are different and their benefits appear to be synergistic rather than simply additive.[20]

The pharmacokinetics of the thienopyridine derivatives have been evaluated to some extent in cats and dogs. However, clinical trials evaluating their efficacy in preventing thromboembolic disease are lacking. Boudreaux and colleagues evaluated the effect of ticlopidine in dogs and identified that ticlopidine at 62 mg/kg was effective in inhibiting adenosine diphosphate and collagen-induced platelet aggregation without detectable effects on AT activity or fibrinogen.[21] Additionally, this same group identified some beneficial effects of ticlopidine therapy in ameliorating pulmonary lesions in an experimental canine model of heartworm disease.[22]

More recently, the effects of ticlopidine and clopidogrel were evaluated in cats.[23,24] Ticlopidine had the most consistent antiplatelet effects at the high dosage (250 mg PO q12h), but at this dosage was associated with anorexia and vomiting.[24] In contrast, clopidogrel resulted in antiplatelet activity at a dosage as low as 18.75 mg/cat q24h, and no clinically significant side effects were observed.[23]

187.4.3 Glycoprotein IIb/IIIa Antagonists

The final class of antiplatelet drugs is the glycoprotein IIb/IIIa antagonists. These drugs are very platelet specific. They bind the integrin primarily responsible for von Willebrand factor attachment to platelets and, as such, block a final common end point in platelet activation and aggregation.[5] Three glycoprotein IIb/IIIa antagonists are available and approved by the U.S. Food and Drug Administration, including eptifibatide, abciximab, and tirofiban. These have been designed for intravenous infusion and have been used most widely in patients with acute coronary syndromes. The oral formulations have been disappointing to date, although research is ongoing in attempts to improve their duration of action and bioavailability.[25]

One veterinary study has examined the effect of abciximab on thrombus formation and platelet function in cats.[26] This study concluded that abciximab was effective at inhibiting platelet function in cats. Of interest, a letter to the editor of the *Journal of Veterinary Internal Medicine* in 2002 by the authors of that study reported an unacceptably high mortality rate associated with another glycoprotein IIb/IIIa antagonist, eptifibatide, and thus its use cannot be recommended in cats.[27]

In humans, dietary supplementation with fish oils rich in n-3 fatty acids, including eicosapentaenoic acid and docosahexaenoic acid, has been documented to alter platelet function. Other benefits of n-3 fatty acid therapy include attenuation of inflammation and alterations in lipid metabolism, which are also beneficial in humans with coronary artery disease. The effects of purified n-3 fatty acids administered orally to cats has also been evaluated, but no significant changes in platelet function were noted.[28,29]

187.5 ORAL ANTICOAGULANTS

Oral anticoagulants act by inhibiting coagulation factors. The most widely used oral anticoagulant is warfarin (coumarin). Ximelagatran, a direct thrombin inhibitor, has a favorable safety and monitoring profile, and its use may ultimately surpass that of the coumarin family. Warfarin acts to inhibit factors II, VII, IX, and X, as well as proteins C and S. Initial exposure to warfarin may result in a temporary procoagulant state due to the shorter half-lives of proteins C and S (endogenous anticoagulants) and, as a result, most protocols include the coadministration of heparin during the induction phase of warfarin therapy. Most veterinarians are very familiar with warfarin toxicity because of its (and subsequent generations') widespread use as a rodenticide. In regard to anticoagulation therapy, warfarin is likely the most effective anticoagulant in dogs. However, it may be very challenging to adjust the dosage appropriately to prevent either insufficient or excessive anticoagulation. Warfarin therapy typically is monitored using the international normalized ratio (INR), a method that assigns levels of reactivity to various thromboplastins, thus permitting comparisons across time and among various laboratories (Box 187-1). One method for successful anticoagulation with warfarin was described by Monnet and Morgan in 2000.[30] This paper described three separate loading doses for large breed dogs and recommended that the most rapid anticoagulation could be obtained with 6 mg q24h.[29] Practically, the long-term use of warfarin in dogs and cats should be considered challenging at best. Frequent rechecks are indicated when therapy is commenced, and clinically significant hemorrhage remains a possibility, even months after iniation of therapy. However, should true anticoagulation be required, the most effective anticoagulant is warfarin. Because the pharmacokinetics of warfarin are altered by numerous other drugs, concurrent drug therapy should be evaluated before initiating therapy. 799

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Ximelagatran (Exanta) is a direct thrombin inhibitor that is used in Europe in humans. Despite favorable safety profiles, including less hemorrhage and no need for frequent monitoring, it is not available in the United States. One limited study in dogs treated with ximelagatran suggested that the direct thrombin inhibitor might be useful in this species.[31] There is no information about its use in cats.

187.6 PARENTERAL ANTICOAGULANTS

The parenteral anticoagulants include unfractionated and low-molecular-weight heparins (LMWH). Unfractionated heparin acts synergistically with endogenous AT and leads to the inactivation of factors II, IX, X, XI, and XII. Inhibition of factors II (thrombin) and X is the most important action. Unfractionated heparin typically is administered at a dosage that prolongs the activated partial thromboplastin time (aPTT) by 1.5 to 2.5 times the baseline result. This approach provides titration of therapy guided by the length of clotting times and not necessarily by achieving an assumed anticoagulant state. The latter is better gauged by measurement of anti-Xa activity.

Because of inherent differences in patient metabolic rates and absorption, effective dosages can not be predicted. Thus frequent monitoring is required. With inadequate dosages, therapy is likely ineffective, and at high dosages, the risk of bleeding is substantial. Another important point is that the therapeutic effect of unfractionated heparin is dependent on an adequate concentration of AT, which can be quite variable in critically ill dogs.

One study evaluated the effects of heparin alone and in combination with fresh frozen plasma in a group of dogs with a variety of critical illnesses and demonstrated an actual decrease in AT activity, which suggests that heparin allowed AT to participate and become consumed in anticoagulant reactions.[32] Another study evaluated the use of heparin and plasma in dogs with immune-mediated hemolytic anemia with respect to PTE, and no difference was detected between the study population and historical controls.[33] In light of these studies, further work is needed to determine the optimal heparin regimens in critically ill dogs. Recommendations include careful monitoring of aPTT and exercising particular caution in dogs judged at risk for hemorrhage (e.g., severely thrombocytopenic).

LMWH represents a fractionated form of heparin designed to have better bioavailability and more predictable anticoagulant activities, and to require less monitoring. LMWH potentiates the activity of antithrombin in a manner similar to unfractionated heparin but results in the preferential inactivation of factor X over thrombin.

In humans, LMWH may be self-administered once or twice a day with little concern for hemorrhagic complications. Monitoring of the aPTT is not required, although evaluation of the anti-Xa activity may be warranted. Although anti-Xa activity analysis is not widely available, it is performed at the Cornell Comparative Coagulation Laboratory. An often-cited target of anticoagulation is achieving an anti-Xa activity of 0.35 to 0.7 U/ml.[33]

Dosing recommendations for LMWH vary significantly according to brand and preparation. Unfortunately, much of the work in evaluating LMWH in dogs and cats has been done in healthy individuals, which probably does not reflect the anticoagulant requirements in hypercoagulable states.[34-36] In regard to the use of LMWH in clinical cases, there is a single published retrospective study describing the use of dalteparin in cats and it suggests that dosages between 100 and 150 U SC q12-24 h in cats with cardiomyopathy were safe; however, efficacy could not be assessed.[37]

The use of LMWH in cases at risk for disseminated intravascular coagulation is also of interest, and preliminary work suggests that the margin of safety may be lower in these cases because of increased incidence of clinical bleeding.[38] It is clear that the ultimate role of LMWH in veterinary patients requires further investigation and has yet to be determined.[39]

187.7 CONCLUSION

Anticoagulant therapy is a growing field in critical care medicine. Moreover, an increasing body of evidence suggests that thromboembolic complications contribute significantly to the overall morbidity and mortality in critically ill patients. The most appropriate agent for the various situations remains undetermined, but will most likely depend on elucidation of the pathogenesis of the thromboembolic condition, our ability to monitor and titrate therapy, and clinical experience.

187.8 Suggested Further Reading*

LI Good, AM Manning: Thromboembolic disease: physiology of hemostasis and pathophysiology of thrombosis. *Comp Cont Educ Pract Vet*. **25**, 2003, 650, *A nice review of hemostasis, particularly as it relates to critically ill patients*.

MA McMichael: Primary hemostasis. *J Vet Emerg Crit Care*. **15**, 2005, 1, *Excellent overview of platelet function*.

DF Hogan, DA Andrews, HW Green, et al.: Antiplatelet effects and pharmacodynamics of clopidogrel in cats. *J Am Vet Med Assoc*. **225**, 2004, 1406, *Research study evaluating clopidogrel in cats*.

ML Keyes, JE Rush, KE Knowles: Pulmonary thromboembolism in dogs. *J Vet Emerg Crit Care*. **3**, 1993, 23, *An earlier review of PTE in dogs*.

DR Phillips, PB Conley, U Sinha, et al.: Therapeutic approaches in arterial thrombosis. *J Thromb Haemost*. **3**, 2005, 1577, *A review paper describing the approach to people affected with arterial thrombosis*.

SA Smith, AH Tobias, KA Jacob, et al.: Arterial thromboembolism in cats: acute crisis in 127 cases (1992-2001) and long-term management with low-dose aspirin in 24 cases. *J Vet Intern Med*. **17**, 2003, 73, *Retrospective analysis of ATE in cats; special mention to ultra–low-dose aspirin use*.

* See the CD-ROM for a complete list of references

188 Chapter 188 Thrombolytic Agents

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188.1 KEY POINTS

- Thrombolytic agents are used to return patency to obstructed blood vessels and improve blood flow to infarcted organs.
- The thrombolytic process occurs primarily on recently formed thrombi because older thrombi have extensive fibrin polymerization that makes them more resistant to thrombolysis. Therefore the use of thrombolytic agents carries the greatest chance for success if these agents are administered as early as possible following identification of a thrombus.
- Thrombolytic agents are used frequently in emergency situations and are commonly associated with complications such as bleeding and reperfusion injury.
- The thrombolytic agents most commonly used in veterinary medicine include tissue plasminogen activator, streptokinase and urokinase.
- There is very little clinical experience with these agents in veterinary medicine. Additionally, these agents are quite expensive, which may limit their clinical usefulness.

188.2 INTRODUCTION

Thrombolysis is the dissolution of thrombi within the cardiovascular system through the enzymatic breakdown of fibrin (fibrinolysis) by the serine protease plasmin. Endogenous thrombolysis is mediated by tissue plasminogen factor (t-PA), which is synthesized in the vascular endothelial cells and facilitates the conversion of plasminogen to active plasmin. Plasmin formation takes place in an intimate association among t-PA, plasminogen, and fibrin. Endogenous thrombolysis via t-PA is modulated by multiple substances, of which plasminogen activator inhibitor and thrombin-activatable fibrinolysis inhibitor are the most notable.

Therapeutic thrombolysis is used for conditions including venous thrombosis, pulmonary embolism, systemic arterial occlusive disease, ischemic stroke, and acute myocardial infarction (Box 188-1). Supraphysiologic levels of exogenous plasminogen activators are administered intravenously to cause thrombus dissolution. The thrombolytic process works primarily on recently formed clots; older thrombi have extensive fibrin polymerization that makes them more resistant to thrombolysis. Therefore the use of thrombolytic agents carries the greatest chance for success if administered as early as possible following identification of a thrombus.

Multiple agents have been approved for use in people for treatment of pathologic thromboses, including streptokinase, urokinase, anisoylated plasminogen streptokinase, t-PA, and modified forms of t-PA (reteplase and tenecteplase). These agents vary with respect to pharmacokinetics, fibrin specificity, thrombolytic activity, and clinical response. However, there is not a tremendous amount of experience with these agents in veterinary medicine, and scientific reports are limited to streptokinase, urokinase, and t-PA.

188.3 SPECIFIC THROMBOLYTIC AGENTS

188.3.1 Streptokinase

Streptokinase combines with plasminogen to form an activator complex that converts plasminogen to the proteolytic enzyme plasmin. Plasmin degrades fibrin, fibrinogen, plasminogen, coagulation factors, and streptokinase. The streptokinase-plasminogen complex converts circulating and fibrin-bound plasminogen and is therefore considered a nonspecific activator of plasmin. This results in a systemic proteolytic state that may predispose to bleeding from loss of coagulation factors and fibrinogen and increase in fibrin degradation products. Although the half-life of streptokinase is relatively short (30 minutes), hypofibrinogenemia can persist for 24 hours.[1]

Streptokinase is produced by streptococci, which can lead to antigenic stimulation within the patient, especially with repeated administrations. Anisoylated purified streptokinase activator complex is a combination of streptokinase and plasminogen that does not require free circulating plasminogen to be effective. Although it does have many theoretic benefits over streptokinase, antigenic stimulation may still occur. This product has not been investigated in clinical veterinary patients.

Streptokinase is typically administered by giving 90,000 IU IV over 1 hour followed by an infusion of 45,000 IU/hr for up to 12 hours (dogs and cats). Currently, the smallest amount of streptokinase that can be purchased is 750,000 IU (estimated cost of $300), which would provide over 15 hours of infusion time. Once reconstituted, it must be used within 8 hours if stored at 2° to 8° C (35.6° to 46.4° F).

188.3.2 Urokinase

The renal tubular epithelium, not endothelium, appears to be the primary in vivo source of the proteolytic enzyme urokinase or urokinase plasminogen activator (u-PA). Urokinase is similar in activity to streptokinase but is considered more fibrin specific because of the physical characteristics of the compound. Commercial preparations, derived from human fetal cell cultures, consist of both high-molecular-weight (HMW) and low-molecular-weight (LMW) fractions. Although the HMW fraction predominates, it is converted quickly and continuously within the circulation to the LMW form, which exhibits greater binding characteristics to the lysine-plasminogen form of plasminogen.[2,3]

188.3.2.1 Box 188-1 Recommendations for Thrombolytic Therapy

188.3.2.1.1 Clinical Scenarios in Which Thrombolytic Therapy Should Be Considered*

Infarction of organs causing life-threatening consequences

- Cerebral infarction
- Complete bilateral renal infarction
- Complete splanchnic infarction
- Symptomatic and progressive pulmonary embolism

Infarction that may cause irreversible organ dysfunction

- Severe bilateral infarction of the pelvic limbs
- Complete unilateral renal infarction
- Severe unilateral infarction of a thoracic or pelvic limb

Infarction with severe clinical consequences that cause owners to consider euthanasia

188.3.2.1.2

Clinical Scenarios in Which Thrombolytic Therapy Could Be Considered

Incomplete infarction of pelvic or thoracic limbs

Symptomatic but static (nonprogressive) pulmonary embolism

188.3.2.1.3

Clinical Scenarios in Which Thrombolytic Therapy Should Not Be Considered

Suspected or proven coagulopathies, thrombocytopenia

Evidence of active bleeding

Infective endocarditis

Intracavitary (cardiac) thrombi

Vascularly invasive neoplastic processes

*Some thrombotic states may require surgical intervention instead of thrombolytic therapy.

Lysine-plasminogen, in contrast to the glutamate-plasminogen form, differentially accumulates within thrombi, thereby conferring fibrin specificity to the u-PA. Additionally, glutamate-plasminogen is converted to lysine-plasminogen during thrombolysis, thereby increasing the binding of u-PA to plasminogen within the thrombus. It is interesting to note that for u-PA to interact with many cell types, including epithelial cells, the high-affinity u-PA receptor (u-PAR) is required.[4,5] HMW u-PA, but not LMW u-PA, binds to u-PAR, and u-PA associated with the u-PAR is susceptible to the physiologic inhibitor plasminogen activator inhibitor, suggesting a possible clearance mechanism.[6,7]

It also appears that u-PA associated with u-PAR is mostly involved in nonproteolytic activities such as cellular adhesion and migration.[8] Prourokinase, a relatively inactive precursor that must be converted to urokinase before it becomes active in vivo, is under investigation in humans. It is inactive in plasma and does not bind to or consume circulating inhibitors. As with tissue-type plasminogen activator (t-PA), prourokinase is somewhat thrombus specific, because the presence of fibrin enhances the conversion of prourokinase to active urokinase by an unknown mechanism. This fibrinolytic agent has not yet been studied in clinical veterinary patients.

Urokinase is available as a lyophilized product in 250,000-IU vials. The manufacturer recommends reconstituting with 5 ml of sterile water and then further diluting the stock solution with 0.9% sodium chloride to a volume of 195 ml. This contains the total dosage for humans. A loading dose is given over 10 minutes, followed by a 12-hour infusion period. Urokinase has been administered to cats and dogs using a protocol of 4400 IU/kg loading dose given over 10 minutes, followed by 4400 IU/kg/hr for 12 hours.[9,10] The average sized cat (4.54 kg) would require approximately one 250,000-IU vial, and a 20-kg dog would require approximately five vials. With a cost of approximately $500 per vial, this translates into an approximate cost of $500 per cat and $2500 per dog for a 12-hour infusion period, respectively.

188.3.3 Tissue Plasminogen Activator

t-PA is the primary activator of plasmin in vivo; however, it does not readily bind circulating plasminogen and therefore does not induce a systemic proteolytic state. Plasminogen and t-PA both have a high affinity for fibrin, thereby forming an intimate relationship within thrombi, resulting in a relatively fibrin-specific conversion of plasminogen to plasmin. However, the fibrin specificity is relative and when t-PA is given at high dosages, a systemic proteolytic state and bleeding can be seen.[11] Although the half-life of t-PA is very short (2 to 3 minutes), a sustained fibrinolytic state may persist, resulting from protection from the physiologic inhibitors or fibrinolysis (plasminogen activator inhibitor, thrombin-activatable fibrinolysis inhibitor).[12]

The recommended dosing protocol for human recombinant t-PA in cats is an intravenous constant rate infusion of 0.25 to 1 mg/kg/hr for a total dosage of 1 to 10 mg/kg.[13] Although the clinical experience in dogs is very limited, one dog received multiple 1-mg/kg intravenous boluses every 60 minutes and another received one intravenous dose of 1 mg/kg administered over 60 minutes.[14,15] It would appear reasonable to parallel the cat treatment protocol of 0.25 to 1 mg/kg/hr IV for a total dosage of 1 to 10 mg/kg.

Activase is supplied in 50-mg and 100-mg bottles with an estimated cost of $1500 and $3000, respectively. Smaller amounts of t-PA can be purchased (Cathflo Activase, Genentech, South San Francisco, CA) for approximately $100 per 2 mg. This may be more cost effective for small cats or dogs and allow owners who have budget constraints to attempt the low end of the dosage range. For example, a typical cat weighing 4.5 kg could receive 2.2 mg/kg for about $500. An average sized dog (15 kg) would require from 15 mg to 150 mg at an approximate cost of $800 to $4500, respectively.

The concentration of t-PA is 1 mg/ml when reconstituted and is good for up to 8 hours when stored at 2° to 8° C (35.6° to 46.4° F). t-PA has been frozen in a regular freezer (–20° C) for up to 6 months without losing thrombolytic activity in an in vitro cat whole blood thrombus model.[16] This may allow unused portions of the drug to be stored and administered to other animals later. This has been done routinely by ophthalmologists to remove fibrin from within the anterior chamber of the eye. However, there are no preservatives in the final solution, so sterility cannot be guaranteed.

188.4 ADVERSE EFFECTS OF THROMBOLYTIC THERAPY

The most common and predictable complication of thrombolytic therapy in humans is bleeding, which may be confounded 802 803 by thrombocytopenia, platelet dysfunction, hypofibrinogenemia, a systemic lytic state, dissolution of hemostatic plugs, or disruption of altered vascular sites.[1,17-20] Fibrin specificity does not appear to have a large clinical effect based on human trials, where the incidence of bleeding was similar between humans treated with streptokinase and t-PA.[20] Intracranial hemorrhage, which is the most concerning bleeding complication, is seen more commonly in patients treated with high levels of t-PA.[19] The reasons for this are not known exactly, but abnormal vascular sites are suspected based on an increased risk in patients of advanced age.[20]

Reperfusion injury can be seen when metabolic waste and electrolytes are released from infarcted tissues. This most commonly occurs in humans who develop arrhythmias after receiving thrombolytic therapy for acute myocardial infarction. The degree of reperfusion injury is proportional to the amount of infarcted tissue, and the more clinically relevant comparison with veterinary medicine may be Leriche syndrome, in which there is infarction of the distal aorta causing ischemia of the pelvic limb musculature. Thrombolytic therapy in these patients results in severe metabolic acidosis and hyperkalemia that often requires aggressive therapy, including hemofiltration or hemodialysis. Similar results are seen with thrombolytic therapy in cats with distal aortic infarction from cardiogenic emboli.[9,13,21,22]

Streptokinase has some specific adverse effects, including hypotension and allergic reactions. Allergic reactions result from antistreptokinase antibodies and there is an increased risk with repeated exposures. The antistreptokinase antibodies may also reduce the efficacy of the drug. For these reasons, streptokinase is not administered to humans more frequently than every 4 years. Such data and guidelines are absent in veterinary medicine.

188.5 THROMBOLYTIC THERAPY IN DOGS

188.5.1 Streptokinase

There is very little reported experience with thrombolytic therapy in dogs. Ramsey and colleagues described a case series of four dogs with thromboembolic disease (one pulmonary, three distal aorta) treated with streptokinase.[23] Partial resolution of the thrombus was noted in one dog, and the other three had complete resolution after one to three doses of streptokinase. All animals experienced partial or complete resolution of clinical signs, with only minor bleeding seen in three that resolved with discontinuation of the streptokinase infusion. There was no evidence of reperfusion injury in this study.

188.5.2 Urokinase

Whelan et al[10] described u-PA use in four dogs. Distal aortic infarction was identified with abdominal ultrasonography in three of the dogs, and pulmonary embolism was diagnosed by echocardiography in one dog. The three dogs with aortic infarction had femoral arterial pulses and voluntary motor function before u-PA administration, and there was no identifiable difference following u-PA therapy. Additionally, there was persistence of the thrombi on abdominal ultrasonography. Even though there was no beneficial effect from u-PA therapy in these three dogs, one dog did develop hyperkalemia and metabolic acidosis suggestive of reperfusion injury. The dog with pulmonary embolism was reported to have benefited clinically with improved echocardiographic indexes, suggesting partial resolution of the pulmonary embolism following u-PA therapy.

188.5.3 Tissue Plasminogen Activator

There are two reports of t-PA therapy for dosage with aortic infarction in the literature. In one case there was a return of femoral arterial pulses after 10 doses of 1-mg/kg bolus injections given every 60 minutes.[14] However, pulses were again absent 6 days after therapy. Pulses returned after an additional two doses of t-PA, and pulse quality improved after two more doses were given within 24 hours. Short-term follow-up revealed persistence of femoral arterial pulses, normal pelvic limb gait, and resolution of the thrombus on abdominal ultrasonography.

The second case was from a study reporting distal aortic infarction in six dogs.[15] All six dogs failed to improve with the administration of 1 mg/kg of t-PA over a 60-minute period with concurrent heparin therapy.

188.6 THROMBOLYTIC THERAPY IN CATS

More clinical data are available for cats because of the higher frequency of cardioembolic disease in this species. The frequency of hyperkalemia and reperfusion injury following embolus dissolution with thrombolytic therapy ranges from 40% to 70%.[13,21,22] Reperfusion injury represents the most common cause of death in cats receiving thrombolytic agents, with survival rates ranging from 0 to 43%.[9,13,21,22] Cats that have more complete infarction, such as causes bilateral paralysis, appear more likely to develop hyperkalemia and metabolic acidosis, probably related to the larger area of ischemia.[13,21]

188.6.1 Streptokinase

There are two retrospective studies evaluating streptokinase therapy for aortic infarction in cats. The first study evaluated eight cats and all experienced respiratory distress and died suddenly during the maintenance phase of streptokinase therapy.[22] However, two of these cats did have intracavitary thrombi within the left atrium, which is generally considered a contraindication for thrombolytic therapy. One of these cats was diagnosed as having a right coronary arterial infarction on necropsy that may have resulted from fragmentation of the left atrial thrombus induced by the thrombolytic therapy.

The second study evaluated 46 cats treated for cardioembolic disease.[21] In this study, approximately 50% had a return of femoral pulses within 24 hours of initiating streptokinase therapy. Motor function returned in 30% of the cats, and 80% regained motor function within 24 hours. Cats with single-limb infarction did dramatically better, with 100% regaining pulses and 80% regaining motor function. Of those cats that had infarction of both limbs, only about 50% regained pulses and approximately 25% regained motor function. Adverse effects were seen in 65% of cats that developed abnormal coagulation parameters after beginning streptokinase therapy. However, some of these cats were also receiving heparin.

Spontaneous bleeding from oral, rectal, or catheter sites was seen in 24% of cats, including 36% of those with abnormal coagulation parameters. Bleeding was severe enough to require transfusions in 27%, with only 18% of these cats surviving streptokinase therapy. Increased respiratory rates were seen in 30% of cats, although this was caused by worsening of congestive heart failure in 21% of the small number of cats in which the underlying cause was pursued (14 of 46). Hyperkalemia developed in approximately 40% of cats and was more likely to be seen with longer infusion periods, which may be related to more complete or severe obstruction. There was an overall survival rate of 33% during hospitalization. However, about 50% of the cats that did survive the hospital stay were euthanized because of complications of therapy or poor prognosis.

188.6.2 Urokinase

There is one retrospective study reporting the use of u-PA for cardioembolic disease in 12 cats.[9] Bilateral aortic infarction was present in 10 of 12 (83%), with no palpable pulse in the affected limb(s) in 10 of 12 (83%) and no motor function in 9 of 12 (75%). Urokinase infusion resulted in the return of pulses in 3 of 10 (30%) and motor function in 5 of 9 (56%). It is interesting to note that more cats regained motor function than had return of pulses, suggesting that collateral circulation and not thrombolysis resulted in the return of function in at least some cats. Hyperkalemia developed in 3 of 12 (25%), including 3 of 7 (43%) that did not have return of pulses or function (again possibly suggesting a role for collateral circulation). There was no evidence of clinical bleeding. Five out of 12 cats survived (42%), and all nonsurvivors were euthanized.

188.6.3 Tissue Plasminogen Activator

There has been one clinical trial of t-PA therapy in six cats with cardioembolic disease.[13] Complications included minor hemorrhage from catheter sites (50%), fever (33%), and reperfusion injury (33%). The acute survival rate was 50%, with deaths attributable to reperfusion injury and cardiogenic shock. Of the cats that survived, 100% had infarction of both limbs. Perfusion was restored within 36 hours and motor function returned within 48 hours in 100% of surviving cats.

188.7 FUTURE DIRECTIONS

The use of rheolytic thrombectomy machines (e.g., AngioJet system) for rapid removal of pathologic thrombi is under investigation in veterinary medicine. Only one study has been published thus far describing the use of this technology in cats with aortic thromboembolism; successful thrombus dissolution was achieved in five of six cats, and three survived to discharge.[24] Surgical thrombectomy may also be indicated in some animals, especially those with organ infarction (e.g., splenic infarction). Further thrombus prevention in animals with thrombotic disease, regardless of the species or cause, remains a controversial subject in veterinary medicine (see Chapter 187, Anticoagulants).

188.8 SUGGESTED FURTHER READING*

KE Moore, N Morris, N Dhupa, et al.: Retrospective study of streptokinase administration in 46 cats with arterial thromboembolism. *J Vet Emerg Crit Care*. **10**, 2000, 245, *The first relatively large (>6 cats) published study describing streptokinase therapy for arterial thromboembolic disease in cats. The paper that dispelled the myth that streptokinase was not safe in cats*.

PD Pion, MD Kittleson: Therapy for feline aortic thromboembolism. In RW Kirk (Ed.): *Current veterinary therapy X*. 1989, Saunders, Philadelphia, *The first description of thrombolytic therapy in domestic animals and the only clinical report of t-PA therapy in cats with arterial thromboembolic disease*.

CC Ramsey, DP Burney, DK Macintire, S Finn-Bodner: Use of streptokinase in four dogs with thrombosis. *J Am Vet Med Assoc*. **209**, 1996, 780, *The first and only clinical description of streptokinase therapy for thromboembolic disease in dogs*.

MF Whelan, TE O'Toole, DL Chan, JE Rush: Retrospective evaluation of urokinase use in cats with arterial thromboembolism. *J Vet Emerg Crit Care*. **15**, 2005, S8,(abstract) *The only clinical report of urokinase use in cats with arterial embolic disease*.

MF Whelan, TE O'Toole, DL Chan, JE Rush: Retrospective evaluation of urokinase use in dogs with thromboembolism (4 cases: 2003-2004). *J Vet Emerg Crit Care*. **15**, 2005, S8,(abstract) *The only clinical report of urokinase use in dogs with thromboembolic disease*.

* See the CD-ROM for a complete list of references

189 Chapter 189 Digoxin

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189.1 KEY POINTS

- Beneficial effects of digoxin administration result from direct actions on cardiac muscle (increase in intracellular calcium) and indirect mediation of the autonomic nervous system.
- Net results of digoxin administration include an increase in force and velocity of myocardial systolic contraction (positive inotropic effect), decrease in activation of the sympathetic nervous and renin-angiotensin-aldosterone systems (neurohumoral deactivation effect), and reduction in heart rate and in conduction velocity through the atrioventricular node (vagomimetic effect).
- Clinically digoxin's main uses are in treating systolic dysfunction that results in congestive heart failure (CHF), including dilated cardiomyopathy and end-stage left ventricular volume overload CHF, and for ventricular rate control in treating supraventricular tachyarrhythmias (atrial fibrillation, paroxysmal atrial tachycardia, atrial flutter).
- Common toxic side effects of digoxin include gastrointestinal disorders (vomiting, diarrhea, anorexia), azotemia, ventricular arrhythmias, and bradycardia.
- Serum digoxin levels should be monitored in all treated patients.

189.2 INTRODUCTION

Controversy has surrounded the use of digoxin since its “modern day” recognition by William Withering in 1785. Withering described the use of the foxglove plant, *Digitalis purpurea* (digitoxin), in treating ascites and peripheral edema in humans. Earlier reports of digitalis use can be found as far back as the thirteenth century.[1] The use of digitalis glycosides has been embroiled in controversy for years. Part of the controversy is influenced by the relatively low therapeutic-to-toxic ratio of these products, including the common digitalis glycoside, digoxin, in use today. The controversy is also influenced by variations in individual response to the drug, marked variation in expression of the side effects, and difficulty in proving clinical efficacy in numerous drug trials.[1] In any event, digoxin is still found on the pharmacy shelf of almost every veterinary facility in existence. It is used mainly to treat heart failure due to systolic dysfunction and to control supraventricular tachyarrhythmias.

189.3 PHARMACOLOGY

Digoxin is extracted from the leaves of the foxglove plant *Digitalis lanata*. The digoxin molecule is composed of a sugar and a cardenolide; its molecular formula is $C_{41}H_{64}O_{14}$ and its molecular weight is 780.95 Da. Digoxin exists as odorless white crystals that are insoluble in water or ether, slightly soluble in alcohol, and freely soluble in pyridine. Digoxin (Lanoxin) is supplied as tablets in either 125 μg (0.125 mg) or 250 μg (0.25 mg) strengths; as capsules in (solution) 100 μg (0.1 mg) or 200 μg (0.2 mg) strengths; as an elixir of 50 μg/ml (0.05 mg/ml); or for intravenous injection as a sterile solution in 2-ml ampules at 250 μg (0.25 mg) per ml or 100 μg (0.1 mg) per ml.[2]

Digoxin's mechanisms of action are multifaceted and include positive inotropic effects that are mediated through its inhibition of sodium-potassium adenosine triphosphatase pumps located on myocardial cell membranes, which results in an increase in intracellular sodium concentration. This sodium in turn is exchanged for extracellular calcium, raising the concentration of available calcium ions within the myocardial cell and thus mediating increased contractility. Digoxin also reduces sympathetic nerve activity, renin-angiotensin activity, circulating catecholamines, and regulates baroreceptor function by increasing vagal tone (vagomimetic effect). These functions are thought to beneficially counteract increases in activity of these systems seen in heart failure.[1] These vagomimetic effects also decrease the rate of sinus node discharge, atrial conduction, and atrioventricular (AV) nodal conduction by prolonging conduction times and refractory periods of these tissues, thereby forming the basis for digoxin's effectiveness at controlling ventricular response to supraventricular arrhythmias.[3]

189.4 PHARMACOKINETICS

Digoxin is readily absorbed, undergoes minimal hepatic metabolism, and is excreted almost entirely by the kidneys. In the dog the serum half-life is 23 to 39 hours, and in the cat it is somewhat more variable and reportedly ranges between 63 and 81 hours.[4,5] Patients with clinical cardiac disease in general have lower serum half-life values than those for normal controls.[4] Based on these values, oral maintenance therapy should provide therapeutic serum levels in dogs in 2 to 5 days and in cats in approximately 8 to 10 days.

189.5 CLINICAL USE

The primary indication for digoxin therapy is heart rate reduction, particularly when associated with rapid ventricular response in patients in atrial fibrillation. It is almost never necessary in veterinary medicine to administer digoxin as an intravenous solution, except as a third-line drug to treat sustained supraventricular tachycardia. Supraventricular tachyarrhythmias are often life threatening and may require acute therapy with 805
intravenous calcium channel blockers, β-blockers, or precordial thump procedures, whereas digoxin can be used as 806
a primary or ancillary drug for long-term management of supraventricular tachycardia.

189.5.1 Box 189-1 Digoxin Dosage Recommendations

- Canine dosage: 0.005 mg/kg PO q12h, 0.005 to 0.011 mg/kg/hr IV to effect.
- Feline dosage: 0.007 mg/kg PO q48h or 0.0035 mg/kg PO q24h.
- Dosing should be based on an estimate of lean body weight.
- Do not exceed an oral dosage of 375 μg (0.375 mg) PO q24h. regardless of body weight.
- Serum digoxin levels should be obtained in all patients.

IV, Intravenous; *PO,* per os.

In general, digoxin is a maintenance medication used for long-term management of systolic dysfunction or supraventricular tachycardia; it is rarely a first-line drug in an acute emergency. If therapeutic levels are needed rapidly, the oral maintenance dosage can be doubled for the first two doses. Digoxin should not be used in patients with significant bradyarrhythmias and should be used with caution in accessory pathway–type tachyarrhythmias because accelerated retrograde conduction may occur.

In a patient with systolic dysfunction, digoxin is almost always accompanied by diuretics, vasodilators, or angiotensin-converting enzyme (ACE) inhibitors for managing congestive heart failure (CHF). Rarely will a significant increase in fractional shortening be seen on echocardiography following digoxin therapy. Digoxin's potentially beneficial primary autonomic action may represent its most significant benefit in severe heart failure.[6] End-stage cardiac diseases with exhausted cardiac reserve are unlikely to respond to inotropic stimulation with digoxin, and serious life-threatening systolic dysfunction may be better managed with other positive inotropic agents such as dobutamine, amrinone, or pimobendan (see Chapters 35 and 36, Cardiogenic Shock and Left Ventricular Failure, respectively).

In choosing a digoxin dosage, it is important to remember that other drugs including diuretics, antiarrhythmics, angiotensin-converting enzyme inhibitors, and calcium channel blockers are likely to increase serum digoxin concentrations. The estimated digoxin dosage should be reduced by 25% if quinidine, verapamil, diltiazem, ibuprofen, aminoglycoside antibiotics, or tetracyclines are being administered concurrently. In addition hypokalemia or hypomagnesemia, or both, are likely to accentuate digoxin toxicity. The oral dosage of digoxin for the dog should not exceed 375 µg (0.375 mg) q12h regardless of body weight (Box 189-1).

Careful monitoring of renal function and electrolytes is always required when using digoxin, and serum digoxin levels should be obtained in all patients to maximize therapeutic success. In dogs serum levels should be measured 5 to 7 days after initial therapy, 6 to 8 hours after dosing. In cats levels should be measured 10 days after initial oral therapy, 8 hours post dose. Serum digoxin levels above 2.5 ng/ml generally are considered to represent toxicity and there is no clinical advantage to be gained by increasing the dosage to obtain values above this level, even in the face of deteriorating systolic performance.

Digoxin's major effect on the surface electrocardiogram is to prolong the PR interval, sometimes creating first-degree AV heart block. This alone, without other signs of toxicity, is not a reason to reduce the dosage. A ventricular arrhythmia that develops following initiation of digoxin therapy should be treated as an adverse side effect until proven otherwise and is grounds for temporary withdrawal of the drug. A sudden increase in serum digoxin levels or sudden onset of signs of toxicity in a previously stable patient receiving long-term therapy warrants immediate assessment of renal function.

189.6

CORRECTING DIGOXIN TOXICITY

As previously mentioned, a ventricular arrhythmia that develops following initiation of digoxin therapy should be treated as an adverse side effect until proven otherwise and is grounds for temporary withdrawal of the drug. Other common signs of toxicity include anorexia, nausea, vomiting, diarrhea, and bradycardia.

Most cases of digoxin toxicity will respond to 48-hour withdrawal of oral administration, and this strategy followed by reinstitution at a lower dosage (50% to 75% of the initial dosage) is usually successful in eliminating adverse reactions. Occasional patients are intolerant of digoxin at any level. Serum electrolyte levels should be normalized and renal function supported as indicated. If ventricular arrhythmias are present, they should be treated appropriately (see Chapter 47, Ventricular Tachyarrhythmias). An antiarrhythmic medication such as lidocaine may be indicated in severe cases. Administration of activated charcoal is indicated for acute accidental ingestion. If life-threatening digoxin toxicity is present, intravenous administration of digoxin-specific antibodies, such as digoxin immune Fab (ovine; Digibind), should be considered.[7]

189.7 SUGGESTED FURTHER READING*

C Bulton, DR Gross, JT Johnston, et al.: Pharmacokinetics, bioavailability and dosage regimens of digoxin in dogs. *Am J Vet Res*. **41**, 1998, 1230, *An article that is helpful in elucidating the therapeutic efficacy of digoxin*.

MD Kittleson: Management of heart failure. In MD Kittleson, RD Kienle (Eds.): *Small animal cardiovascular medicine*. 1999, Mosby, St. Louis, *A chapter that covers digoxin extensively, with a large number of references that are helpful for further study*.

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* See the CD-ROM for a complete list of references

190 Chapter 190 Antiarrhythmic Agents

Kathy N. Wright, DVM, DACVIM (Cardiology)

190.1 KEY POINTS

- Antiarrhythmic agents are useful for managing various tachyarrhythmias, but the clinician must have knowledge of the patient, the arrhythmia, and the indications for and side effects of each medication.
- Drugs that prolong atrioventricular (AV) nodal refractoriness are useful for AV node–dependent and atrial arrhythmias, whereas drugs that prolong myocardial refractoriness are used in atrial, accessory pathway, and ventricular tachyarrhythmias.
- Most antiarrhythmic agents have multiple channel effects, not simply those of their Vaughan-Williams class. This must be considered in predicting their potential beneficial and adverse effects.
- Disappointing results in the ability of antiarrhythmic agents to prevent sudden death have emerged from several large-scale human studies, and this goal now largely falls into the realm of device or catheter-based therapy. Antiarrhythmic agents can be useful in limiting clinical signs related to tachyarrhythmias, thus potentially preventing euthanasia of veterinary patients.

190.2 INTRODUCTION

Antiarrhythmic agents have undergone critical reevaluation during the past 10 to 15 years with the publication of large-scale human studies that brought to light some of the risks and shortcomings of drug therapy for arrhythmias.[1,2] Once more cavalier in their use of these agents, veterinarians and physicians alike are having to analyze carefully the potential benefits and risks (including proarrhythmic effects) in each patient. Basically, there are two reasons to treat arrhythmias: (1) to alleviate significant clinical signs such as weakness, syncope, or precipitation or exacerbation of congestive heart failure by an arrhythmia, and (2) prolonging survival. Antiarrhythmic drugs, in general, have not been shown to do the latter; this predominantly falls into the realm of antiarrhythmic devices. Drugs can be very useful, however, in alleviating clinical signs in an individual patient.

190.3 CLASSIFICATION SCHEMES

No completely satisfactory or intuitive classification scheme for antiarrhythmic agents has been developed. The most commonly used is the Vaughan-Williams classification system, which attempts to group drugs according to their major ion channel or receptor effects. The limitations of this system have been well documented, including the fact that most antiarrhythmic drugs act on multiple channels or receptors, and one must know that when predicting their beneficial and adverse effects. The actions of antiarrhythmic drugs are actually very complex and vary according to species (important to veterinarians because much of the data are from humans), age, tissue drug concentration, acid-base and electrolyte balance, presence or absence of myocardial damage, and indirect hemodynamic or autonomic actions.[3]

190.3.1 Box 190-1 Antiarrhythmic Agent General Uses

190.3.1.1 Drugs Used to Manage Ventricular Tachyarrhythmias

Class Ia: procainamide, quinidine

Class Ib: lidocaine, mexiletine

Class Ic: flecainide, propafenone

Class II: β-blockers: atenolol, propranolol

Class III: d,l-sotalol, amiodarone

190.3.1.2 Drugs Used to Manage Supraventricular Tachyarrhythmias

190.3.1.2.1 Drugs Used to Slow Atrioventricular Nodal Conduction

Class II: β-blockers: atenolol, propranolol

Class IV: calcium channel blockers

Other: digoxin

190.3.1.2.2 Drugs to Inhibit Intramyocardial Conduction or Prolong Myocardial Repolarization

Class Ia: procainamide

Class Ic: flecainide, propafenone

Class III: d,l-sotalol, amiodarone

In spite of its shortcomings, the Vaughan-Williams system remains the most widely used to date. An attempt to improve on this system led electrophysiologists to develop the Sicilian Gambit in 1991.[4] This approach attempted to identify the vulnerable parameter for various arrhythmias and did account for the multiple channel and receptor actions of each antiarrhythmic agent, but was too unwieldy for widespread general use.

Grouping antiarrhythmic agents into their main uses (i.e., supraventricular arrhythmias, ventricular arrhythmias) would seem logical (Box 190-1), but many agents are used for multiple arrhythmias, hence overlap would be inevitable. Despite its inherent limitations, the Vaughan-Williams classification is used as the framework for this chapter. Agents that are commonly used in small animal cardiology are discussed.

190.4 CLASS I ANTIARRHYTHMIC AGENTS

Class I agents act primarily by inhibiting the fast sodium channel and decreasing the slope of phase 0 of the action potential. The relative potency of their sodium channel effects, whether blockade of the activated or inactivated channel occurs, and their effects on other channels and receptors determine their subclassification.

190.4.1 Class Ia Antiarrhythmic Agents

Class Ia agents have powerful, fast sodium channel–blocking effects and also exhibit moderate blockade of the rapid component of the delayed rectifier potassium current (I_{Kr}). This I_{Kr} blockade results in action potential prolongation and can account for the proarrhythmic effects associated with these drugs in some genetically predisposed individuals.[5] In addition, potent depression of conduction velocity can predispose to the reentrant phenomenon. Quinidine, procainamide, and disopyramide are class Ia drugs.

Procainamide is the prototypical agent of this class used in small animal cardiology. It depresses conduction velocity and prolongs the effective refractory period in a wide variety of tissues, including the atrial and ventricular myocardium, accessory atrioventricular (AV) pathways, and retrograde fast AV nodal pathways.[5] Procainamide can thus be effective in a wide variety of arrhythmias, either as a single agent or combined with other agents. It can be administered parenterally for acute termination of severe ventricular or supraventricular tachyarrhythmias. It must be administered slowly intravenously (over 5 to 10 minutes) to prevent hypotension.

Agents that prolong AV nodal conduction time are given first for acute treatment of atrial tachyarrhythmias, because procainamide can enhance AV nodal conduction, thus worsening the ventricular response rate. Procainamide is more effective than lidocaine for acutely terminating these rhythms in human patients.[6] Parenteral procainamide is administered in doses of 6 to 8 mg/kg IV over 5 to 10 minutes or 6 to 20 mg/kg IM in dogs. A constant rate infusion (CRI) of 20 to 40 µg/kg/min can be used once a therapeutic response is obtained with bolus administration. Parenteral procainamide in cats is used cautiously at dosages of 1 to 2 mg/kg IV or 3 to 8 mg/kg IM and a CRI of 10 to 20 µg/kg/min.

Adverse effects commonly are associated with procainamide but appear to be more frequent in humans and cats than in dogs. Gastrointestinal side effects such as anorexia, nausea, and vomiting are seen most commonly in dogs. Side effects reported in humans soon after procainamide is instituted include rash and fever. Later side effects include arthralgia, myalgia, and agranulocytosis. The development of systemic lupus erythematosus is identified rarely in veterinary patients, but is reported in one third of human patents who take procainamide for longer than 6 months.[7] A four-way trial of antiarrhythmic drugs in Boxer dogs with ventricular tachyarrhythmias showed that procainamide administered at 20 to 26 mg/kg PO q8h. reduced the frequency of ventricular ectopy but did not alter the frequency of syncope.[8]

190.4.2 Class Ib Antiarrhythmic Agents

Class Ib antiarrhythmic agents inhibit the fast sodium channel, primarily in the open state with rapid onset-offset kinetics. The window sodium current is also inhibited, resulting in shortening of action potential duration in normal myocardial tissue. Their rapid kinetics explain why class Ib agents have minimal effects on the shorter atrial action potential. The ability of lidocaine and its congeners to block I_{Na} is enhanced in the presence of acidosis, increased extracellular potassium concentrations, and partially depolarized cells. Thus these drugs selectively suppress automaticity and slow conduction velocity in ischemic and diseased ventricular myocardium.

Lidocaine is an intravenous antiarrhythmic agent and is typically the first drug used in the acute treatment of serious ventricular tachyarrhythmias in dogs. It has the benefit of minimal hemodynamic, sinoatrial, and AV nodal effects at standard dosages. A bolus dose of 2 to 4 mg/kg is administered IV over 2 minutes. The bolus can be repeated to a maximum of 8 mg/kg within a 10-minute period, provided adverse effects do not occur. If successful in converting the ventricular tachycardia to sinus rhythm, a lidocaine bolus can be followed by a CRI of 25 to 75 μg/kg/min.

Hepatic clearance of lidocaine determines its serum concentration, and this is directly related to hepatic blood flow. Heart failure, hypotension, and severe hepatic disease can therefore result in decreased lidocaine metabolism and predispose the patient to lidocaine toxicity. The incidence of side effects in cats is much higher, with earlier reports of bradyarrhythmias and sudden death; for this reason, caution is recommended. Lower dosages of 0.25 to 0.75 mg/kg are administered slowly IV, followed by infusion rates of 10 to 20 μg/kg/min.

The most common adverse effects of lidocaine include nausea, vomiting, lethargy, tremors, and seizure activity. These typically resolve quickly with cessation of the infusion. Diazepam may be administered to treat lidocaine-induced seizures.

Mexiletine is the most commonly used oral class Ib agent in dogs. It is highly protein bound and eliminated by renal excretion. Its use and side effect profile mirror those of lidocaine. It has been used in dogs in which ventricular tachyarrhythmias are acutely responsive to lidocaine and can be combined with class Ia, II, or III agents. Typical dosing in dogs is 4 to 8 mg/kg PO q8h. There are no data on its use in cats. Tocainide, another lidocaine congener, rarely is used in small animals because of the high incidence of serious side effects, including renal failure and corneal dystrophy.[9,10]

190.4.3 Class Ic Antiarrhythmic Agents

Limited to no data are available on these agents in clinical veterinary medicine. Their expense, propensity for proarrhythmia in humans with structural heart disease, and negative inotropic properties have dampened enthusiasm for exploring their use in veterinary patients.

190.5 CLASS II ANTIARRHYTHMIC AGENTS

β-Adrenergic antagonists, or β-blockers, are some of the most universally useful cardiovascular drugs. β-Blockers have even found their way into the management of dilated cardiomyopathy, a disease for which they were once thought strictly contraindicated. In human patients with stable controlled heart failure, β-blockers reduce all-cause, cardiovascular, and sudden death mortality rates.[11-13] The clinician must be ever cognizant of the animal's underlying heart disease when prescribing β-blockade, however, because this will determine the tolerance of the drug and how slowly it must be introduced. As antiarrhythmic agents, class II agents (1) inhibit the current I_f, an important pacemaker current that also promotes proarrhythmic depolarization in damaged cardiomyocytes, and (2) 808 809 inhibit the inward calcium current, $I_{Ca\text{-}L}$, indirectly by decreasing tissue cyclic adenosine monophosphate levels. The magnitude of their antiarrhythmic effect depends on the prevailing sympathetic tone, with an increased effect in higher adrenergic states.

β-Adrenergic antagonists are used to slow AV nodal conduction in supraventricular tachyarrhythmias, slow sinus nodal discharge rate in inappropriate sinus tachycardia (such as that associated with pheochromocytomas), and suppress ventricular tachyarrhythmias thought to be caused, at least in part, by increased sympathetic tone. Their ability to slow AV nodal conduction appears to be inferior to those of the calcium channel blockers or class IV agents in the dog.[14] β-Blockers are often used as first-line antiarrhythmic agents in cats with ventricular or supraventricular tachyarrhythmias. They are often combined with class I or class III agents in dogs with severe ventricular tachyarrhythmias.

β-Blockers are contraindicated in patients that have evidence of sinus nodal dysfunction (sinus arrest, sinoatrial block, persistent sinus bradycardia), AV nodal conduction disturbances, pulmonary disease (particularly true with nonspecific β-blockers or high-dose β_1-selective blockers), or overt congestive heart failure.[5] Fluid retention must be evaluated in patients with congestive heart failure and their condition must be stabilized before β-blockade is instituted. Extremely low dosages must be used in patients with systolic myocardial dysfunction and a course of very slow up-titration followed. Thus, in this subclass of patients, β-blockers are not the choice for acute antiarrhythmic therapy, because the amounts required are not generally tolerated.

The drug that is used can vary according to the situation and clinician's preference. Esmolol is the intravenous class II agent of choice in small animal cardiology because of its short half-life. A comparison of intravenous negative dromotropic agents in normal dogs showed that esmolol was a significantly less effective negative dromotrope than diltiazem and caused a severe drop in left ventricular contractility measurements at dosages required to prolong AV nodal conduction.[14] Esmolol is given as an intravenous bolus over 1 to 2 minutes at 0.5 mg/kg. This can be followed by a CRI of 50 to 200 μg/kg/min. Continuous careful monitoring of the electrocardiogram and blood pressure must be performed during administration of this drug.

The most commonly used oral β-blockers in small animals are atenolol and metoprolol, given their relative β_1 selectivity and long half-life compared with those of propranolol. Heart rate monitoring is useful to determine the appropriate dosage of β-blocker for an individual animal. Atenolol is water soluble and eliminated by the kidney, and metoprolol undergoes hepatic metabolism and elimination. These pharmacokinetic differences should be remembered in choosing a β-blocker and dosage for a particular patient.

190.6 CLASS III ANTIARRHYTHMIC AGENTS

These drugs block the repolarizing I_K, resulting in prolongation of action potential duration and effective refractory period. Although this effect is beneficial if it occurs at tachyarrhythmia rates, the intrinsic problem is that most class III agents block the rapid component of the I_{Kr} rather than the slow component (I_{Ks}); thus their effects are accentuated at slower heart rates. This puts the patient at risk of early afterdepolarization and accounts for the proarrhythmic effect of class III antiarrhythmic drugs. This risk is increased with concurrent hypokalemia, bradycardia, intact status in females, increasing age, and macrolide antibiotics.[15] Amiodarone, with its block of both I_{Ks} and I_{Kr}, makes the action potential pattern more uniform throughout the myocardium and has the least reported proarrhythmic activity of the class III agents.

The two class III agents used in small animal cardiology are sotalol and amiodarone, both of which have multiple channel and receptor effects. d,l-Sotalol combines nonselective β-blockade with I_{Kr} inhibition. It is an effective antiarrhythmic agent in both supraventricular and ventricular tachyarrhythmias. Its class II effects predominate at lower dosages and include sinus and AV nodal depression. Its class III effects, seen at higher dosages (>160 mg q24h in humans) are prolongation of the atrial and ventricular myocardial action potential, prolongation of the atrial and ventricular refractory periods, and inhibition of bidrectional conduction along any bypass tract. Prolongation of the action potential duration can result in enhanced calcium entry during the action potential plateau and may explain why the negative inotropic effect of sotalol is far less than expected. Sotalol is hydrophilic, nonprotein bound, and excreted solely by the kidneys. The same absolute and relative contraindications apply to sotalol as to general β-blockers.

Two studies of Boxer dogs with familial ventricular arrhythmias compared d,l-sotalol with other antiarrhythmic agents. In the first study, dogs were grouped into asymptomatic, syncopal, and heart failure groups. The dosage of sotalol administered to these dogs was 0.97 to 6.1 mg/kg Po q24h, divided q12h, titrated to effect. Syncopal signs diminished on sotalol therapy, and dogs with systolic dysfunction did not appear to suffer untoward drug effects.[16] The second study compared four antiarrhythmic drug regimens for familial ventricular arrhythmias of Boxers. Sotalol 1.47 to 3.5 mg/kg PO q12h. significantly reduced the maximum and minimum heart rates, number of PVCs, and ventricular arrhythmia grade. No significant change in the occurrence of syncope, however, was found for sotalol or for any of the other three treatments studied.[8] Sotalol typically is administered at 1 to 2 mg/kg PO q12h in dogs and cats.

Amiodarone is the antiarrhythmic agent with the broadest spectrum, exhibiting properties of all four antidysrhythmic antiarrhythmic classes. It opposes electrophysiologic heterogeneity, which underlies some severe ventricular arrhythmias. The efficacy of amiodarone exceeds that of other antiarrhythmic compounds, including sotalol, in human patients. Furthermore, the incidence of torsades de pointes with amiodarone is much lower than expected from its class III effects.

A major drawback is that amiodarone is associated with a host of multisystemic, potentially serious side effects that sotalol is not. A retrospective report of Doberman Pinschers with severe ventricular tachyarrhythmias receiving amiodarone documented adverse effects in 30% of the 20 patients studied.[17] These adverse effects included vomiting, anorexia, hepatopathies, and thrombocytopenia, and were more common with higher maintenance dosages. Amiodarone typically is reserved for life-threatening ventricular or supraventricular tachyarrhythmias that are not responding to other therapy. Published amiodarone dosages in dogs vary and typically include a loading period.[18] The author usually uses 15 mg/kg q24h for 7 days, then 10 mg/kg q24h for 7 days, then 5 mg/kg q24h long term. Serum amiodarone levels can be measured but may not correlate with tissue concentrations. Amiodarone has not been used in cats.

190.7 CLASS IV ANTIARRHYTHMIC AGENTS

This is the group of calcium channel–blocking drugs. Nondihydropyridine calcium channel blockers slow AV nodal conduction and prolong the effective refractory period of nodal tissue. This effect is most notable at faster stimulation rates (use dependence) and in depolarized fibers (voltage dependence).[3] These drugs are effective in slowing the ventricular response rate to atrial tachyarrhythmias and can prolong the AV nodal effective refractory period to the point that an AV node–dependent tachyarrhythmia is terminated. They are generally contraindicated in wide-complex tachyarrhythmias.

Diltiazem has gained preference over verapamil because of its more favorable hemodynamic profile (i.e., minimal negative inotropic effect) at effective antiarrhythmic dosages. Intravenous diltiazem (0.125 to 0.35 mg/kg slowly IV over 2 minutes) has been used in dogs to acutely terminate a severe AV nodal dependent tachyarrhythmia or slow the ventricular response rate to an atrial tachyarrhythmia. A comparison of the electrophysiologic and hemodynamic responses of intravenous diltiazem, esmolol, and adenosine in normal dogs demonstrated the superior efficacy of diltiazem in slowing AV nodal conduction while maintaining a favorable hemodynamic profile.[14]

Standard oral diltiazem is administered three times daily, which can be difficult particularly for cat owners. Sustained-release preparations, however, appear to have more variable absorption in companion animals, with resultant poorer arrhythmia control. Such preparations also have had a high incidence of side effects reported in cats, including vomiting, inappetence, and hepatopathies.[18]

190.8 OTHER ANTIARRHYTHMIC AGENTS

190.8.1 Digoxin

The electrophysiologic effects of digoxin are primarily indirect through the autonomic nervous system by enhancing central and peripheral vagal tone. This results in slowing sinus nodal discharge rate, prolonging AV nodal refractoriness, and shortening the atrial refractoriness. Digoxin is used orally as an antiarrhythmic agent to slow AV nodal conduction in dogs, particularly those with impaired left ventricular systolic function. The ventricular rate is almost never slowed adequately with digoxin as a single agent, however, and other drugs must be added. The dosage range is 0.005 to 0.01 mg/kg PO q12h in a normokalemic dog with normal renal function, and 0.0312 mg PO q24-48h in a normokalemic cat with normal renal function.

Digoxin has a narrow therapeutic index; owners must be educated on the signs of toxicity. Renal dysfunction, hypokalemia, advancing age, chronic lung disease, and hypothyroidism all predispose to digoxin toxicity and should be corrected (if possible) or the dosage adjusted downward. Serum digoxin concentrations should be monitored to get the appropriate dosage for an individual animal. The trend in human medicine is toward lower dosages, which appear to be safer and confer benefit with less risk of toxicity. The ideal blood levels remain unknown, but an aim of about 0.5 to 1 ng/ml or 0.6 to 1.2 nmol/L (much lower than before) seems reasonable.[19]

190.8.2 Adenosine

Adenosine is used widely in the emergency department in human patients to terminate AV nodal dependent tachyarrhythmias. A study performed by the author showed that adenosine, even at dosages of 2 mg/kg, was ineffective in slowing canine AV nodal conduction.[14] The same result has been found with electrophysiologic study in numerous dogs with orthodromic AV reciprocating tachycardia. A similar study has not been performed in cats.

190.9 ANTIARRHYTHMIC DEVICES AND PROCEDURES

Certain supraventricular tachyarrhythmias in dogs can be cured, rather than simply controlled, with transvenous radiofrequency catheter ablation.[20] The tachyarrhythmia circuit is first mapped with numerous multielectrode catheters. Once detailed mapping has identified a site in the reentrant circuit or an automatic focus for ablation, a larger-tipped electrode catheter is coupled to a cardiac-specific radiofrequency ablation unit. Radiofrequency energy is delivered to the tip electrode causing thermal dessication of a small volume of tissue to permanently interrupt the tachycardia circuit. This technique has been used by this author and others in a number of canine cases.

Permanent pacemaker implantation is a necessary component of the management of certain bradyarrhythmias, such as permanent high-grade AV nodal block and sick sinus syndrome. Rate responsiveness and dual chamber pacing are all options that are being used or explored by veterinary cardiologists in an attempt to improve quality of life and decrease pacing-related complications. Implantable cardioverter-defibrillators have revolutionized treatment for humans with life-threatening ventricular tachyarrhythmias, playing a crucial role in the prevention of sudden cardiac death related to ventricular tachycardia and fibrillation. These devices have been used experimentally in dogs and in one clinical report.[21]

190.10 SUGGESTED FURTHER READING*

HJ Dargie: Beta blockers in heart failure. *Lancet*. **362**(2), 2003, *An excellent review of the use of β-blockers for heart failure*.

KM Meurs, AW Spier, NA Wright, et al.: Comparison of the effects of four antiarrhythmic treatments for familial ventricular arrhythmias in Boxers. *J Am Vet Med Assoc*. **221**(522), 2002, *An important study that examined various antiarrhythmic regimens and their effects in Boxer dogs with ventricular tachyarrhythmias and identified notable failure of any of these antiarrhythmic drugs to alter the occurrence of syncope*.

NS Moise: Electrocardiography and cardiac arrhythmias. In S Ettinger, B Feldman (Eds.): *Textbook of veterinary medicine*. ed 6, 2005, Saunders, St Louis, *An excellent review chapter of the basic electrocardiogram, arrhythmias, and antiarrhythmic drugs for the small-animal clinician*.

KN Wright, DS Schwartz, R Hamlin: Electrophysiologic and hemodynamic responses to adenosine, diltiazem, and esmolol in dogs. *J Vet Intern Med*. **2**(201), 1998, *An important study that showed the superior negative dromotropic properties and more favorable inotropic profile of intravenous diltiazem compared with esmolol, demonstrating the lack of efficacy of adenosine in dogs*.

* See the CD-ROM for a complete list of references

191 Chapter 191 β-BLOCKERS

Betsy R. Bond, DVM, DACVIM (Cardiology)

191.1 KEY POINTS

- β-Adrenergic blockers are one of our oldest and most commonly used medications in veterinary cardiology, and they have a multitude of uses in many different areas.
- The most common use of β-blockers is for supraventricular and ventricular arrhythmias.
- Although they have been used for systemic hypertension, they are not as effective as other medications.
- Esmolol is one of best β-blockers to use in the critical care setting because it has a short duration of action and can be given in a constant rate infusion.
- β -Blockers should be used with caution in animals with congestive heart failure and systolic dysfunction because of their negative inotropic effects.
- Although β-blockers are administered with increasing frequency in human patients with dilated cardiomyopathy, this use is just now being studied in veterinary medicine. The potential benefits of using β-blockers in dogs with mitral regurgitation are also not known.
- There is controversy about the use of β-blockers in cats with cardiomyopathy.

191.2 INTRODUCTION

For a long time, β-adrenergic receptor blockers have been important treatment options in both human and veterinary medicine, although they have only been used to manage mild to moderate congestive heart failure (CHF) in humans for the last 10 years. The use of β-blockers for heart failure represented a dramatic theoretic change because physicians previously believed that β-blockers were contraindicated in any kind of CHF.[1] Although frequently used for certain cardiomyopathies and arrhythmias in veterinary medicine, β-blockers may be underutilized in dogs and cats with CHF.

On the other hand, they have immense value in the critical care setting because of their usefulness in diverse situations. For example, using the ultra–short-acting drug esmolol for an arrhythmia can test the efficacy of β-blockers without overtly compromising the patient. Once β-blockers have proven beneficial, longer acting agents or a constant rate infusion (CRI) of esmolol may be prescribed.

191.3 PATHOPHYSIOLOGY OF β-ADRENERGIC RECEPTORS

Classically, β-receptors are divided into β_1-receptors, found in the heart muscle, and β_2-receptors, located primarily in bronchial and vascular smooth muscle but also found in cardiac muscle. β_3-Receptors also exist, but because their existence and function in the critical care setting are not well known, they will not be discussed here. β-Receptors are coupled to adenylcyclase by a stimulatory G protein; this coupling causes the formation of cyclic adenyl monophosphate (cAMP). cAMP is a second messenger with two primary effects in the heart muscle: (1) a positive inotropic effect (an increase in the rate and force of myocardial contraction) and (2) a relaxing or lusitropic effect (by facilitating reuptake of calcium into the sarcoplasmic reticulum). In the sinus node there are both chronotropic (increased rate of firing) and dromotropic (accelerated rate of conduction) effects that combine to increase the heart rate.[2] Beta stimulation can also stimulate growth of cardiomyocytes and cause the particularly deleterious effects of myocyte toxicity and apoptosis.[1]

The failing human heart has an increased adrenergic drive, which supports the heart in early, acute stages, but it ultimately causes damage to the myocardium in the chronic state.[1,3] In normal human ventricles the number of β_1-receptors is much greater than β_2-receptors, but the ratio is reversed in failing ventricles because of selective downregulation of β_1-receptors.[1] The altered ratio of β_1 and β_2 receptors has also been shown in a canine model of induced heart failure.[4]

191.4 MECHANISMS OF ACTION

191.4.1 Generations of β-Blockers

Although β-blockers are only one class of drugs, their effects are extremely varied and are determined by their pharmacologic properties: selective versus nonselective, presence or absence of intrinsic sympathomimetic activity, and additional actions (e.g., carvedilol is a nonselective β-blocker with α-adrenergic vasodilatory properties). Division of the various β-blockers is by generations.[2]

First-generation β-blockers are nonselective, blocking both β_1-adrenergic and β_2-adrenergic receptors.[1,2] Propranolol is the prototypical first-generation agent and has been used the longest in veterinary medicine.

Second-generation β-blockers are known as selective β-blockers because at normal dosages they are more cardioselective, acting predominantly on β_1-receptors rather than β_2-receptors. Atenolol and metoprolol are selective β-blockers and have the advantage of generating less bronchospasm or any other side effect that might arise from β_2-blockade.

Third-generation β-blockers such as carvedilol are nonselective and have the additional property of being vasodilators through α_1-blockade.[1,2,5]

β-Blockers are also recognized as class II antiarrhythmic drugs in the Vaughan-Williams classification.

191.4.2 General Cardiovascular Effects

- Stabilize membrane
- Lower sinus heart rate
- Slow atrioventricular conduction
- Diminish cardiac output at rest and during exercise
- Decrease myocardial oxygen demand
- Reduce blood pressure

- Increase airway resistance
- Decrease platelet aggregation[6]

191.5 CAUTIONS AND CONTRAINDICATIONS

Absolute contraindications to the use of all β-adrenergic blockers include[6]:

- Overt, severe CHF (because ofnegative inotropic effects)
- Second-degree and third-degree atrioventricular block
- Sick sinus syndrome[2]
- Sinus bradycardia
- Cardiogenic shock

Relative contraindications include[6]:

- Mild CHF
- Bronchoconstrictive disease (especially nonselectiveβ-blockers)
- Diabetes mellitus (because of the effect on insulin release, again more of a problem in nonselective β-blockers)

Potential adverse effects include[6]:

- Bradycardia
- Hypotension
- Exacerbation of existing CHF

191.6 USES IN VETERINARY MEDICINE

191.6.1 General Uses

- Supraventricular tachyarrhythmias
- Ventricular tachyarrhythmias
- Symptomatic hyperthyroidism
- Hypertrophic cardiomyopathy ([HCM]—especially the obstructive form)
- Systemic hypertension

- Pheochromocytoma[7]

191.6.2 Arrhythmias

β-Blockers have been used to manage both ventricular and supraventricular arrhythmias in dogs and cats, but they are used more commonly in cats than in dogs, and more in supraventricular than ventricular arrhythmias. There are more studies about the use of β-blockers in cats than in dogs.[8] There are fewer studies concerning use of β-blockers for monotherapy in dogs because they are not effective when used as a sole agent.[9]

Rate control is one of the main factors in managing both supraventricular tachycardia and ventricular tachycardia, and the agent of choice is the one that works. β-Blockers should be among the first drugs used in supraventricular tachycardia because (1) they are relatively safe, (2) the ultrashort-acting preparations can be used as a test dose without undue harm to the patient, and (3) if the short-acting form is effective then a CRI may be instituted to maintain longer antiarrhythmic control. Another advantage of β-blockers in the acute setting is the wide variety of oral drugs that may be used for long-term management. Although they are not as effective against ventricular tachycardia as other drugs are, β-blockers should be part of the critical care specialists' ready stock of antiarrhythmic agents.

191.6.3 Hyperthyroidism

Hyperthyroidism is probably one of the most commonly diagnosed diseases in cats, having been well described since the 1970s.[10] With the common use of radioactive iodine and antithyroid medications such as methimazole and propylthiouracil, β-blockers are not necessary for treatment of thyrotoxicosis. However, they are still useful in treating thyroid storm and as a bridge to other therapies.[10,11]

191.6.4 Feline Cardiomyopathies

The controversy with β-blockers started in 1991 when a small number of cats were treated with either propranolol or diltiazem, and the cats treated with propranolol had shorter life spans.[12] The controversy continued with Fox's study in cats with both HCM and CHF. His results showed that cats treated with atenolol and furosemide did worse than cats treated with either furosemide and diltiazem or furosemide and enalapril.[13] The difficulty in interpreting these data is that in cats with the obstructive form of HCM, heart rate control is much more effective with atenolol than with diltiazem. Atenolol will often lower or abolish the outflow obstruction, whereas diltiazem tends to do neither. More studies need to be done on this phenomenon.

191.6.5 Congenital Aortic Stenosis

Atenolol has been used in some dogs with symptomatic aortic stenosis. The mechanism of action is similar to that of cats with hypertrophic obstructive cardiomyopathy (HoCM).

191.6.6 Congenital Mitral Stenosis

The benefit of using β-blockers in mitral stenosis comes from slowing the heart rate, allowing more time for ventricular filling.

191.6.7 Systemic Hypertension

Systemic hypertension is common in veterinary medicine, and use of β-blockers was one of the earliest treatments. Unfortunately, they were not very efficacious and have since been overshadowed by amlodipine, a long-acting calcium channel blocker. They are used only for adjunctive drug therapy when multiple medications are needed.[14]

191.6.8 Pheochromocytomas

Pheochromocytomas are rare tumors of the part of the adrenal gland that emits catecholamines, with all of their adverse effects on the heart and vascular system (e.g., tachyarrhythmias and hypertension). In the author's experience and in that of others, most medical therapies are dismal failures. 812 813 β-Blockers may be used after α-blockers, but often both are ineffective.[15]

191.6.9 Canine Dilated Cardiomyopathy

Because of the positive benefits in humans with dilated cardiomyopathy (DCM) and because sympathetic tone is elevated in dogs with DCM,[16] it has been suggested that the latter might also benefit from β-blockers. However, because of the negative inotropic effects and because many dogs with DCM have adverse reactions, most veterinarians are hesitant to use β-blockers. More studies are required in this area.[17]

191.6.10 Mitral Regurgitation

Dogs with CHF secondary to chronic acquired valvular disease (CAVD) have higher plasma norepinephrine than control than in dogs.[16] Whether this would translate into a clinical benefit with β-blockade requires further study.

191.7 INDIVIDUAL AGENTS

Esmolol (Brevibloc) is an ultra–short-acting β_1-blocker that can be used to determine if β-blockers would be effective against a particular arrhythmia. Its primary advantage is its short duration of action, with a distribution half-life of about 2 minutes after an intravenous bolus. If a CRI is started, steady-state levels are reached in about 5 minutes after an initial intravenous bolus, or in 30 minutes with no loading dose. Blood pressure and heart rate should be monitored in patients receiving a CRI.[6]

Propranolol (Inderal) is a nonspecific β-blocker and the first one used in veterinary medicine. Its major disadvantages are that it should be given every 8 hours and that it has more systemic and brochoconstrictive effects than second-generation β-blockers. However, it is also easier to titrate the dosage because of its shorter half-life compared with other oral β-blockers. Propranolol is used in dogs and cats as an antiarrhythmic medication and in cats for HoCM. In the emergency setting it is particularly good for supraventricular tachyarrhythmias and hyperthyroidism.[6]

Atenolol is a selective β-blocker. It has been used in some cats with HCM[18] and HoCM, although there is no hard evidence to support its long-term or short-term benefit.[13] The theoretic basis of a benefit to using β-blockers in cats with HCM or HoCM is that left ventricular hypertrophy causes diastolic dysfunction. By slowing the heart rate, β-blockers increase the filling time, thereby improving diastolic function.[19,20] In cats with HoCM, slowing the heart rate can either lessen or relieve the outflow obstruction that decreases the accompanying mitral regurgitation, which theoretically decreases the potential for pulmonary edema.[20]

Metoprolol has been used in dogs with both DCM and CAVD with a minimum of adverse effects. Survival times were no different between dogs with CAVD and those with DCM, but there were no control dogs that had one of the two diseases and were not treated with β-blockers. There was a significant reduction in heart rate compared with pretreatment values, but there were no differences in echocardiographic parameters. An interesting observation is that dogs with DCM treated with metoprolol had a longer median survival time than dogs with CAVD, although there was no statistical difference.[21] The logical importance is that as a group, dogs with DCM tend to have shorter survival times than dogs with CAVD. Although it is classified as a selective β_1-blocker, metoprolol may lose selectivity at higher dosages.[6]

Carvedilol is a mildly β_1-selective agent that becomes nonselective at higher dosages. It is also a potent α_1-blocker, which accounts for its vasodilating properties.[1] Carvedilol is being studied for its usefulness in dogs with DCM and mitral regurgitation. Its pharmacokinetics have been studied in healthy dogs,[22] although good controlled studies in dogs with congestive heart failure are lacking.[5]

Sotalol is a nonselective β-blocker with class III antiarrhythmic properties. It has about 30% of the β-blocking properties of propranolol.[6] Sotalol has become very popular as an antiarrhythmic drug in Boxers with arrhythmogenic right ventricular cardiomyopathy.[9] Although it works very well for suppressing arrhythmias and preventing syncope, definitive studies have not shown that it prevents sudden cardiac death. Another caution is its use in dogs with DCM and ventricular arrhythmias, in which clinical condition may worsen because of the negative inotropic effects of β-blockers.[6]

191.8

SUGGESTED FURTHER READING*

JA Abbott: Medical management of dilated cardiomyopathy. In Conference Proceedings 2005, ACVIM, Charlotte, NC, June 4-8 *A good overview of management of DCM, including the rationale behind using β-blockers in these patients and in patients with atrial fibrillation.*

SG Gordon: Carvedilol and chronic valve disease. In Conference Proceedings 2004, ACVIM, Minneapolis, MN, June 9-12 *A good overview of not only the use of carvedilol, but also how other β-blockers may be used in dogs with CAVD.*

ME Peterson: Hyperthyroid diseases. In SJ Ettinger, EC Feldman (Eds.): *Textbook of veterinary internal medicine*. ed 6, 2004, Saunders, Philadelphia, *Overview of feline hyperthyroidism.*

JE Rush, LM Freeman, C Hiler, et al.: Use of metoprolol in dogs with acquired cardiac disease. *J Vet Cardiol*. **4**, 2002, 23, *The most comprehensive study of metoprolol in veterinary medicine to date.*

* See the CD-ROM for a complete list of references

192 Chapter 192 Aerosolized Medications

Carrie J. Miller, DVM, DACVIM

192.1 KEY POINTS

- The use of inhaled aerosol medications has stemmed primarily from the need to manage a variety of respiratory diseases in dogs and cats effectively and with minimal side effects.
- Aerosol therapy (also known as *nebulization*) is the production of a liquid particulate suspension within a carrier gas (the aerosol) that is inhaled by the patient. Many factors determine whether an inhaled medication will have the desired effect in its desired location.
- Medicinal aerosolized particles are generally described by their mass median diameter (MMD), defined as the diameter above which 50% of the particle mass number resides.
- The MMD of a particle must be less than 5 μm to reach the small bronchioles and alveoli.
- Three types of systems have been used in veterinary medicine: jet nebulizers, ultrasonic nebulizers, and metered dose inhalers.
- Inhaled bronchodilators and glucocorticoids have been investigated for the treatment of feline bronchopulmonary disease and canine allergic airway diseases.
- Inhaled antibiotics have been investigated for the treatment of canine infectious tracheobronchitis and bacterial pneumonia.
- Although nebulized particles are known to reach the lower airways in cats (and presumably dogs), whether a sufficient number of the particles are deposited in the lower airways using the recommended dosages is unknown.

192.2 INTRODUCTION

Administration of medications via inhalation has been commonplace in human medicine for decades.[1] Only recently has inhalant therapy begun to emerge in veterinary medicine, and its use remains empiric at best. Although few published peer-reviewed studies exist on inhalant medications in dogs and cats, clinical use is clearly on the rise. This chapter will attempt to summarize the principles behind aerosol therapy, describe the various delivery systems, and depict the common respiratory diseases in dogs and cats for which inhalant therapy is prescribed.

192.3 PRINCIPLES OF AEROSOL DEPOSITION IN THE LUNGS

The use of aerosol medication has mainly stemmed from the need to manage a variety of respiratory diseases in dogs and cats effectively and with minimal side effects. Many of the more common respiratory diseases require glucocorticoids and bronchodilators, which can have severe and costly side effects when given systemically. [2,3] In addition, many owners have difficulty administering medications to their cats or dogs, which results in poor owner compliance and inappropriate dosing. Aerosolization may also allow the clinician to effectively manage a disease that may be difficult to treat with systemic medications (e.g., *Bordetella bronchiseptica* infection).[4]

Aerosol therapy (also known as *nebulization*) is the production of a liquid particulate suspension within a carrier gas (the aerosol). Many factors determine whether an inhaled medication will have the desired effect in the correct location. The size of the particle must be small enough to travel to the lower airways. Aerosolized particles generally are described by their aerodynamic equivalent diameter (AED). This is defined as the diameter of a sphere with a standard density of 1 g/cm^3 that falls in air at the same rate as the particle in question.[5] For a particle to be deposited in the small bronchioles and alveoli, it must have an AED of 0.5 to 5 µm. Particles larger than 10 µm usually are deposited in the larynx and nasal turbinates (Table 192-1). The AED is a definition that applies only to aerosols that are homogenous in size, which is not typical of most therapeutic aerosols. Because therapeutic aerosols contain a range of particle sizes (termed *heterodisperse*), the term that is more widely used is mass median diameter (MMD). This is defined as the diameter above which 50% of the particle mass number resides.[6]

Other important factors that affect the deposition of aerosolized particles in the airways include the rate of gravitational fall (gravitational sedimentation), the tendency of the particles to resist change in airflow speed and direction (inertial impaction), and the inherent random motion of particles created by collision with gas molecules (Brownian diffusion). Inertial impaction occurs when there is a sudden change in the direction of gas flow. This is most common in the nasal turbinates and bronchial bifurcations, so it tends to have the most impact in the upper airways with large particles that are greater than 5 µm AED. Gravitational sedimentation has more of an impact in the lower airways where smaller particles travel. Brownian diffusion is thought to affect only particles smaller than 0.1 µm and is probably not clinically relevant.[1,5,6] It is important to remember that the degree of particle deposition by these mechanisms will also depend on patient variables, such as inspiratory air velocity, tidal volume, and ventilatory pattern.[5]

192.4 DELIVERY SYSTEMS

192.4.1 Jet Nebulizers

Compressor (jet) and ultrasonic nebulizers are commonplace in human medicine, and they are becoming more popular for the treatment of dogs and cats as well. The jet nebulizer uses a narrow, high-velocity gas (typically oxygen) stream that travels through the designated medicated solution to comminute the liquid into an aerosol mist.[7] The mist is then delivered to the patient through a spacer and face mask (Color Plates 192-1 and 192-2). 814 Most nebulizers of this type are capable of producing 50 µl of usable aerosol 815 per liter of carrier gas, with an MMD of 3 to 6 µm.[6] This allows a significant portion of the respirable particles to travel to the bronchioles and alveoli, thus settling principally by gravitational sedimentation in the lower airways.

Table 192-1 Site of Aerosolized Particle Deposition in the Respiratory Tree

Site of Deposition	Aerodynamic Diameter (µm)
Nasopharynx	>20
Trachea	10 to 30
Bronchi	5 to 25
Peripheral airways	0.5 to 5

Certain guidelines must be followed for effective nebulization. The nebulizer and face mask should be kept in an upright position to maximize the effect of nebulization. To enhance particle deposition in the lower airways, it is recommended to use a high-output compressor (20 to 30 psi, 8 to 10 L/min). The flow rate will minimize the effects of inertial impaction in the upper airways, and the compressor pressure will ensure adequate particle size as well as decrease the time needed for nebulization. Because inertial impaction can also be affected by the face mask and tubing properties, a shorter tube length, and thus decreased dead space within the nebulizing system, is recommended. Because exhalation into the nebulized mist of medication will decrease the proper delivery of the drug, a one-way inspiratory valve is preferred to maximize drug delivery to the lungs.[5]

Because nebulizers can quickly become contaminated with bacteria and fungi, proper disinfection of all parts must be performed after each use. Disposable nebulizers are not recommended because their efficacy tends to decrease significantly after each use.[5] It is typically recommended that jet nebulizations occur over 5 to 10 minutes.

192.4.2 Ultrasonic Nebulizers

Ultrasonic nebulizers are very similar to the jet nebulizers. The source of particle generation, however, is a piezoelectric transducer crystal that converts electrical energy into ultra–high-frequency oscillations that create aerosol particles from the surface of the liquid. There is no need for a compressor gas setup, so these nebulizers are more portable and are even sold for home use. Although the MMD particle size is similar in the two types of nebulizers (3 to 7 µm for ultrasonic nebulizers), the ultrasonic nebulizers can create a denser mist, with aerosols up to 200 µl/L.[6] One brand of ultrasonic nebulizer that is manufactured for dogs and cats is portable, and owners can be instructed on how to use it at home (Nebulair, DVM Pharmaceuticals, Miami, FL). It is typically recommended that ultrasonic nebulizations occur over 5 to 10 minutes.

192.4.3 Metered Dose Inhalers

Metered dose inhalers (MDIs) have been used in human medicine since 1956.[7] They have allowed for complete outpatient, portable inhalation devices to be used conveniently in human medicine. During the last 20 years, veterinarians have been experimenting with MDIs, and material has been published on how best to use these devices in cats and dogs.[2,8] MDIs consist of a plastic mouthpiece and a holder attached to a sealed aerosol canister, with a metered valve that releases a precisely measured dose of medication when the canister is pressed into the actuator (Color Plate 192-3). Once the device is actuated, the medication is propelled through the nozzle at a high lminivelocity (>30 m/sec) to form a spray.[7]

Because of the high velocity of the spray, and the large MMD, holding chambers have been developed to decrease the velocity and particle size produced from MDI devices. This aids in decreasing the amount of inertial impaction in the upper airways and allows the patient to breathe independently of the actuation of the device. These chambers are termed *spacers* and should be attached to a form-fitting, low–dead-space face mask for veterinary patients. Not only do the spacers provide the aforementioned benefit of decreasing inertial impaction, but they also allow for the mist to be sprayed into the chamber before applying the face mask to the animal patient, thus decreasing the likelihood that the MDI device will scare the animal. Aerosols are delivered rapidly over 1 to 2 minutes, with an average of 7 to 10 breaths suggested. There are two brands of veterinary spacers and face masks manufactured specifically for cats (Aerokat and Nebulair). Another option is to use a human pediatric spacer and face mask, or a veterinary anesthesia face mask.

192.5 CLINICAL APPLICATIONS

192.5.1 Feline Bronchopulmonary Disease

Feline bronchopulmonary disease (FBPD) is a syndrome that encompasses a group of common, although poorly understood, respiratory diseases. Clinical signs are found in dogs with chronic bronchitis. The mainstay of treatment for these inflammatory and allergic respiratory diseases is glucocorticoids and bronchodilators (see Chapter 20, Allergic Airway Disease in Dogs and Cats and Feline Bronchopulmonary Disease).[2,3,9] As stated earlier, these medications often have detrimental side effects: glucocorticoids commonly are associated with polyphagia and subsequent weight gain, polydipsia, polyuria, changes in personality, ulceration of the gastrointestinal tract, immunosuppression, hypercoagulability and diabetes mellitus (with long-term use). Some of the xanthine derivatives (theophylline, aminophylline) can cause vomiting, diarrhea, and inappetence, and all bronchodilators can cause excessive central nervous system stimulation and cardiac arrhythmias.[10] Inhaled medications may allow the clinician to more effectively control signs of these diseases without causing undesirable systemic side effects.

192.5.1.1 Inhaled Bronchodilators

Inhaled β_2-adrenergic receptor agonists (albuterol, salmeterol) commonly are used to manage bronchoconstriction secondary to inflammatory lower airway disease. Stimulation of the β_2-receptor causes an increase in intracellular adenylate cyclase, which decreases intracellular calcium and subsequently causes smooth muscle relaxation of the bronchial wall.[11,12] β_2-Adrenergic receptor agonists have been administered by nebulization experimentally to dogs at high doses and have had minimal systemic effects. In rats, ulcerated mucosal lesions may develop in the rostral aspect of the nasal cavity, but this was not reported in dogs.[13]

Minimal clinical studies exist in the small animal veterinary literature evaluating the use of inhaled β_2-agonists for the management of patients with bronchopulmonary disease. One study showed improvement in lung function following the use of an albuterol inhaler in cats with FBPD.[14] Additional investigators have 815
recommended an albuterol inhaler (88 μg/dose, 2 puffs q12h, 7 to 10 breaths) for cats with moderate to severe 816
signs of feline bronchopulmonary disease. [2,8]

192.5.1.2 Inhaled Glucocorticoids

Inhaled glucocorticoids have been studied extensively in laboratory dogs as a model for human asthma, but there are minimal controlled, randomized studies that evaluate the use of inhalant glucocorticoids in the veterinary clinical setting. Interestingly, there are studies showing that the administration of systemic glucocorticoids for at least 48 hours before inhaled bronchodilators causes a significantly greater sensitivity to subsequent β_2-agonist administration. It is thought that glucocorticoids upregulate β_2-adrenergic receptors on bronchial smooth muscle.[15,16] The newer inhaled glucocorticoids tend to have very low systemic absorption and a longer duration of action due to increased lipophilicity.[5]

Inhaled glucocorticoids (e.g., fluticasone propionate [Flovent]) have been suggested for management of FBP. Use of either a 220 or 110 μg/dose MDI for fluticasone propionate has been suggested.[2,17] The recommended dosage is 2 puffs, with 7 to 10 breaths, twice daily in cats with bronchopulmonary disease.[18] Because it takes approximately 2 weeks to obtain steady-state concentrations with fluticasone propionate, oral glucocorticoids should be administered for at least 2 weeks after starting therapy.[2] At that time, if the cat appears clinically normal, the oral steroids should be tapered slowly. The suggested dosages for commonly used inhaled glucocorticoids and bronchodilators in small animal veterinary medicine are summarized in Table 192-2.

192.5.1.3 Other Inhaled Medications

Ipratropium bromide is an acetylcholine antagonist that helps to relax smooth muscle. It has minimal systemic absorption and minor effects on the inhibition of salivation. It has been used in human medicine in the treatment of patients with bronchitis, although its use for this indication has not been evaluated in veterinary medicine. Cromolyn sodium is an inhaled medication that works to inhibit chloride channels and to inhibit the degranulation of mast cells. Although this has not been used in small animal medicine, it may be useful in cases in which the bronchoconstriction is caused primarily by mast cell and eosinophilic infiltration.[5]

Table 192-2 Published Dosages for Inhaled Medications Commonly Used in Management of Feline Bronchopulmonary Disease

Generic Name	Trade Name	Activity	Dosage
Albuterol	Proventil	β_2-Agonist	88 μg/dose 2 Puffs q12h
Salbutamol	Ventolin	β_2-Agonist	100 μg/dose 2 Puffs q12h
Salmeterol	Serevent	β_2-Agonist	50 μg/dose No published dosage
Fluticasone	Flovent	Glucocorticoid	220 μg/dose 110 μg/dose 2 Puffs q12h
Flunisolide	AeroBid	Glucocorticoid	250 μg/dose 2 Puffs q12h

192.5.2 Canine Infectious Tracheobronchitis and Pneumonia

The most common bacterial agent of infectious tracheobronchitis is *Bordetella bronchiseptica*. This gram-negative bacterium is predominantly extracellular and has several characteristics that allow the organism to attach to the tracheal cilia. This makes it difficult to decrease *Bordetella* numbers with systemic antibiotic therapy.[4] Bemis and others have shown that parenteral antibiotics do not significantly decrease tracheal numbers of *Bordetella*. They were able to show, however, that aerosolized gentamicin did significantly decrease *Bordetella* numbers in experimentally infected dogs.[19] Animals with symptomatic infectious tracheobronchitis that are treated with gentamicin aerosolization may show significant clinical improvement when compared with others that are managed with commonly used oral medications.[20] Systemic absorption of aerosolized gentamicin is minimal (<3%) and does not affect renal parameters.[21] The dosage of gentamicin suggested is 6 to 7 mg/kg diluted 1:3 with sterile saline that is nebulized for 5 to 10 minutes, 2 to 3 times daily, for a minimum of 3 days.[19,20,22]

192.5.3 Medications for Use With Bronchoscopy

One of the more detrimental complications associated with bronchoscopy is bronchospasm, which can result from irritation caused by the bronchoscope itself or can occur during and after a bronchoalveolar lavage. This can be particularly life threatening in patients with preexisting bronchoconstriction. Preventive use of bronchodilators has been evaluated in human medicine and has also been looked at in one study of cats undergoing bronchoscopy.[18] Ipratropium bromide is a bronchodilator that inhibits the acetylcholine receptor on bronchial smooth muscle, resulting in smooth muscle relaxation.[5] This study showed that ipratropium bromide used in combination with salbutamol lowered the incidence of BAL-induced bronchoconstriction and may be recommended as a preventive treatment for cats with presumptive FBPD undergoing bronchoscopy. This study used MDIs for both ipratropium bromide (20 μg/puff, 2 puffs) and salbutamol (100 μg/puff, 2 puffs) in the cats before administration of sedation or anesthesia.

192.6 CONCLUSION

Although nebulized particles are known to reach the lower airways in cats (and presumably dogs), whether a sufficient number of the particles are deposited in the lower airways using recommended dosages remains unknown.[23] However, various clinical studies have suggested that inhaled medications do cause an improvement in clinical signs of respiratory disease in dogs and cats. Perhaps as more controlled prospective studies are performed, the veterinary use of inhalant therapy will become more evidence based than empirically based.

192.7 SUGGESTED FURTHER READING*

DM Boothe: Drugs affecting the respiratory system. In DM Boothe (Ed.): *Small animal clinical pharmacology and therapeutics*. 2001, Saunders, Philadelphia, *Chapter that describes the drugs commonly used in small animal medicine to treat a variety of respiratory diseases. Describes mechanisms of action and adverse side effects on the various organ systems*.

816

817

RB Ford: Canine infectious tracheobronchitis. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. 2006, Saunders, St Louis, *Book chapter that discusses* Bordetella bronchiseptica *as a bacterial agent of canine infectious tracheobronchitis; describes the etiology, pathogenesis, and treatment for* Bordetella bronchiseptica *respiratory infections*.

CE Greene, DJ Watson: Antibacterial chemotherapy. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. 2006, Saunders, St Louis, *A thorough review of antibiotic (i.e., aminoglycoside) pharmacokinetics and administration guidelines*.

CJ Miller: Gentamicin aerosolization for treatment of infectious tracheobronchitis. *Proc J Vet Intern Med*. **17: 27, 2003 (**, 2003, abstract 27) *Abstract that demonstrates in a retrospective manner that gentamicin aerosolization for the treatment of infectious tracheobronchitis can significantly lessen clinical signs, according to the owners of affected dogs; clinical signs reduced in comparison with other oral medications that had been used previously*.

P Padrid: Use of inhaled medications to treat respiratory diseases in dogs and cats. *J Am Anim Hosp Assoc*. **42**, 2006, 165, *Article that describes the pathology behind feline asthma and explains the use of MDIs to treat this disease*.

* See the CD-ROM for a complete list of references

193 Chapter 193 Complications of Chemotherapeutic Agents

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193.1 KEY POINTS

- Chemotherapy is one mode of management for cancer in dogs and cats.
- Recent advances in chemotherapy have resulted in increased remission rates and survival times for patients with cancer.
- Complications of chemotherapy occur, and innocent bystanders are also harmed.
- It is imperative that the clinical staff be aware of toxicities of each chemotherapeutic agent so that complications can be identified.
- Complications should be managed rapidly and thoroughly with supportive measures.

193.2 INTRODUCTION

Cancer is a major cause of disease-related death in dogs and cats. Various studies during the last 30 years show that about half of all dogs and one third of all cats will die of cancer. The prevalence of cancer in small animals is increasing, along with an increased awareness and an expansion of knowledge about diagnosis, management options, and prognosis.[1]

As clinicians strive toward higher remission rates and longer survival times, management protocols are rapidly approaching the “cutting edge.” The consequence of these advances is that chemotherapy complications have become a reality of practice.

Preparation, recognition, and early intervention for such complications is critical for a successful outcome for patients receiving chemotherapy. This chapter will focus on the complications of chemotherapy in dogs and cats.

193.3 PRINCIPLES OF CHEMOTHERAPY

Chemotherapy literally means “the management of illness by chemical means.”[2]

Simply stated, chemotherapy drugs work by killing cells. Categories of chemotherapy drugs include alkylating agents, antibiotics, antimetabolites, enzymes, hormones, nonsteroidal antiinflammatory drugs, platinum products, and vinca alkaloids. Each of these effect cell death by various mechanisms of action and all can cause toxicoses as normal cells, as well as cancer cells, are arbitrarily killed in various body systems.

193.4 CHEMOTHERAPY DRUGS

Alkylating agents include cyclophosphamide, chlorambucil, CCNU (1-[2-chloroethyl]-3 cyclohexyl 1 nitrosourea), BCNU (1,3-bis-[2-chloroethyl]-1-nitrosourea), and melphalan. Antibiotic chemotherapy drugs consist of doxorubicin, actinomycin, epirubicin, bleomycin, and mitoxantrone. Antimetabolites are methotrexate and cytosine arabinoside. L-Asparaginase is an enzyme used in chemotherapy. Nonsteroidal antiinflammatory drugs that commonly are used include piroxicam, meloxicam, deracoxib (Deramaxx), etodolac (EtoGesic), and carprofen (Rimadyl). Prednisone is the hormone most commonly used as a chemotherapeutic agent. Platinum products include cisplatin and carboplatin. Lastly, the vinca alkaloids include vincristine, vinblastine, and vinorelbine.[3–5]

Chemotherapy drugs and their potential toxicoses are listed in Table 193-1.

193.5 TOXICITY AND THERAPY FOR CHEMOTHERAPY EMERGENCIES

193.5.1 Acute Tumor Lysis Syndrome

See Chapter 171, Tumor Lysis Syndrome.

Table 193-1 Chemotherapy Drugs and Potential Toxicoses[4,5,11]

Chemotherapeutic Agent	Reported Toxicosis	Specific Toxicities
Alkylating agents	Alopecia Bone marrow suppression Gastrointestinal toxicity Nausea Inappetence Vomiting Diarrhea	CCNU: Cumulative dosage risk of hepatotoxicity Chlorambucil: Neurotoxicity Cyclophosphamide: Sterile hemorrhagic cystitis
Antibiotics	Alopecia Bone marrow suppression Gastrointestinal toxicity Nausea Inappetence Vomiting Diarrhea Necrosis, ischemia, and severe soft tissue reaction if given perivascularly	Doxorubicin: Cumulative dosage risk of dilated cardiomyopathy in dogs, possible renal toxicity in cats, allergic reactions reported in both species, hemorrhagic colitis
Antimetabolites	Alopecia Bone marrow suppression Gastrointestinal toxicity Nausea Inappetence Vomiting Diarrhea	—
Enzymes	Anaphylaxis	L-asparaginase: Pain on injection, pancreatitis, insulin resistance
Hormones	Iatrogenic excessive hormonal effects	Prednisone: Hypercortisolism
NSAIDs	Gastrointestinal ulceration Renal toxicity	Carprofen: Liver toxicity
Platinum products	Bone marrow suppression Gastrointestinal toxicity Inappetence Nausea Vomiting Diarrhea	Cisplatin: Pulmonary edema and death in cats, nephrotoxicity in dogs
Vinca alkaloids	Alopecia Bone marrow suppression Gastrointestinal toxicity Ileus Peripheral neuropathies	—

CCNU, 1-(2-Chloroethyl)-3 cyclohexyl-1-nitrosourea; *NSAIDs,* nonsteroidal antiinflammatory drugs.

193.5.2

Allergic Reactions

Acute type I hypersensitivity reactions have been reported on administration of L-asparaginase. Polysorbate 80, the carrier found in etoposide, can also trigger a type I reaction. Doxorubicin administration can directly stimulate mast cell degranulation, causing an anaphylactoid reaction. This is in contrast to true hypersensitivity reactions, whereby mast cell degranulation is activated via immunoglobulin E.

Clinical signs in dogs usually appear within minutes of administration and can include head shaking, generalized urticaria, erythema, agitation, vomiting, and hypotension leading to collapse. For the most part, dogs tend to manifest allergic reactions in their skin and gastrointestinal (GI) tract. Although rare in cats, hypersensitivity reactions tend to manifest as respiratory signs such as tachypnea, dyspnea, and wheezing.[6]

Prevention of hypersensitivity reactions can be achieved by pretreatment with histamine H_1 and H_2 blockers. In the emergency setting, therapy should consist of discontinuing the drug, instituting fluid therapy, and administering a H_2 blocker (diphenhydramine) and steroids (dexamethasone). Epinephrine can be given in severe and refractory cases.[6]

193.5.3 Bone Marrow Toxicity

Myelosuppression can occur in the oncology patient for a number of reasons, such as secondary to the neoplastic process or as a result of treatment. For the purposes of this chapter, bone marrow toxicity resulting from the cytotoxic effects of chemotherapy is addressed.

193.5.3.1 Anemia

Anemia is a common hematologic abnormality in patients with cancer and is most often due to a syndrome of anemia of chronic disease, blood loss, or a paraneoplastic syndrome of immune-mediated hemolytic anemia. Anemia is rarely encountered secondary to chemotherapy because of the longer lifespan of red blood cells.[7] Although uncommon, anemia can occur secondary to bleeding into the GI tract due to GI ulceration or chemotherapy. When an animal is bleeding into the GI tract from an ulcer, therapy with antacids and GI protectants is indicated. If the ulceration is due to long-term antiinflammatory use, these should be 818
discontinued. If the bleeding is due to chemotherapy, such as in the case of hemorrhagic colitis secondary to 819
doxorubicin chemotherapy, it is usually short term and rarely causes anemia. Supportive care with GI protectants and antidiarrheal medications can be instituted for comfort. Anemia secondary to recurrent marrow suppression and exhaustion of the marrow usually is seen after months of therapy and is related to repeated insults to the bone marrow; it is considered irreversible.

193.5.3.2 Thrombocytopenia

Thrombocytopenia can result from platelet consumption, destruction, decreased production, or loss. For thrombocytopenia resulting from loss into the GI tract, ulcer therapy with antacids, GI protectants, and discontinuation of antiinflammatory drugs is recommended. Thrombocytopenia that results from chemotherapy is rarely of clinical significance and may be treated by delaying chemotherapy for 3 to 5 days. Thrombocytosis can be seen in patients after chemotherapy due to bone marrow rebound in response to chemotherapy-induced thrombocytopenia.[7]

193.5.3.3 Neutropenia

Neutropenia most often is associated with cytotoxic chemotherapy agents. This type of myelosuppression occurs at the nadir, which is defined as the time when the white blood cell count is at its lowest after administration of chemotherapy. The nadir is different for each drug; the nadir for doxorubicin and cyclophosphamide is 7 to 10 days, for cisplatin 7 and 16 days, and for carboplatin, the nadir is 11 and possibly 21 days after administration. In many instances, treatment is not required for neutropenia because the patient is asymptomatic and the cell counts likely will return to the normal range within a week.

Neutropenia in an oncology patient, even one without a fever, should direct the veterinary staff to recommend careful monitoring of vital signs (temperature, pulse, and respirations), appetite, and attitude. Neutrophil counts below 1000 cells/µl warrant prophylactic therapy with broad-spectrum antibiotics for a week. If at any time the patient develops a fever or the clinical condition deteriorates (inappetence, lethargy, depression, vomiting, diarrhea), aggressive intervention is required to prevent a septic crisis. This should start with a complete physical examination with an emphasis on auscultation of the lungs, basic blood work and urinalysis, and administration of fluid therapy, in addition to four-quadrant protection with antibiotics (gram-negative, gram-positive, aerobic, and anaerobic coverage). Strict aseptic technique should be used at all times. Additional supportive therapies should be administered as indicated.

Neutropenia that is profound or persists for over 1 week necessitates therapy with granulocyte colony-stimulating factor. This should be instituted in the hospital for up to 5 days.

193.5.4 Sepsis

Sepsis and septic shock are not uncommon in patients with cancer. Sepsis can be the result of the disease itself or a complication of management (see Chapters 106 and 107, Sepsis and Septic Shock, respectively).

193.5.5 Cardiotoxicity

See Chapter 38, Canine Cardiomyopathy.

193.5.6 Dermatologic Toxicity

Dermatologic complications can occur secondary to chemotherapy but rarely require emergency or critical care attention and therefore is not be discussed in this chapter.

193.5.6.1 Extravasation

Extravasation of vesicant chemotherapeutic agents can cause severe local tissue reactions leading to necrosis. Doxorubicin is the chemotherapeutic agent most commonly responsible and arguably results in the most severe reactions, but this may be due to the volume that is extravasated. Other chemotherapeutic agents such as the vinca alkaloids and other anthracyclines can also be locally irritating if delivered outside the vein. Clinical signs of pain, pruritus, erythema, moist dermatitis, and necrosis can occur within 7 to 10 days with doxorubicin and within a week if a vinca alkaloid has extravasated.[6]

If doxorubicin is given accidentally outside the vein, the following recommendations apply[3]:

1. Discontinue administration of the drug immediately.
2. Withdraw as much drug as possible from the catheter.
3. Administer dexrazoxane at 10 times the extravasated dose intravenously within 3 hours of the event and then daily for 3 days.[8]
4. Monitor the site every other day for 10 days for local tissue reaction.

5 Treat any local reaction symptomatically: topical preparations (antibiotics, steroids), bandaging, Elizabethan collar, and surgical debridement if severe.

If a vinca alkaloid is delivered outside the vein, the following recommendations apply[6]:

1 Discontinue administration of the drug immediately.

2 Withdraw as much as possible from the catheter.

3 Some oncologists infiltrate the area with sterile saline or sterile saline and 8.4% sodium bicarbonate and 4 mg dexamethasone sodium phosphate.

4 Apply warm compress.

5 Treat any local reaction symptomatically: topical preparations (antibiotics, steroids), bandaging, Elizabethan collar, and surgical debridement if severe.

193.5.7 Gastrointestinal Toxicity

Some of the common ongoing health complaints of the oncology patient include cancer cachexia, anorexia, vomiting, and diarrhea.

193.5.7.1 Cachexia and Anorexia

Cachexia and anorexia are common complications of chemotherapy.[8,9]

193.5.7.2 Vomiting

Vomiting is a common consequence of chemotherapy. Although it is usually self-limiting within 2 to 3 days after it starts, routine supportive care can improve the patient's comfort and shorten the duration of this side effect. If the patient does not stop vomiting within a 24-hour period or is vomiting unrelentingly, more aggressive treatment is recommended. This would include fluid therapy, intravenous antiemetics (metoclopramide in a constant rate infusion or dolasetron), and possibly esophageal and GI protectants such as slurry of sucralfate and intravenous ranitidine if esophagitis is considered a risk. 819

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193.5.7.3 Diarrhea

In oncology patients that are stressed by their treatment or hospitalization, clostridial colitis can result. This condition is characterized by a small volume of loose stool that may or may not have frank blood and mucus in it. Historically, it has been diagnosed on a fecal smear by identification of clostridial endospores in conjunction with clinical signs. An enzyme-linked immunosorbent assay kit is now available for detection of *Clostridium perfringens* endospores in fecal specimens. The recommended antimicrobial therapy for clostridial diarrhea is based on sulfasalazine, metronidazole, ampicillin, or tylosin. Dietary management by increasing fiber content in the food by addition of canned pumpkin or psyllium hydrophilic mucilloid fiber (Metamucil) is also recommended. In mild cases of diarrhea, treatment with bismuth subsalicylate (Pepto-Bismol) will often result in resolution of signs within a day or so.

Hemorrhagic colitis is a unique toxicity of doxorubicin (Adriamycin). This form of large bowel diarrhea usually will respond to sulfasalazine or metronidazole. If the diarrhea is moderate to severe, persists for longer than 2 to 3 days, or if the patient is exhibiting signs of lethargy, depression, fever, vomiting, or general malaise, more aggressive intervention with hospitalization, resting of the GI tract, fluid therapy, and antibiotics is recommended.

193.5.8 Neurologic Toxicity

Peripheral neuropathies have been reported after administration of the vinca alkaloids, particularly vincristine. Hind limb weakness, partial paralysis, and ileus leading to abdominal pain and constipation have been reported in dogs and cats.[6,7] Therapy includes supportive care and alleviating the discomfort of ileus with metoclopramide. Oftentimes, discontinuation of the drug or administering it at a reduced dosage is required.

Cisplatin has resulted in cortical blindness in a case report of 2 dogs.[7] 5-Fluorouracil is extremely neurotoxic in cats and should never be administered; it results in a fatal reaction that includes excitability, blindness, tremors, dysmetria, and death. In dogs, it can also result in excitation, seizures, and ataxia.[7]

193.5.9 Urologic Toxicity

Cyclophosphamide has been associated with sterile hemorrhagic cystitis characterized by clinical signs including pollakiuria, hematuria, and dysuria. Historical administration of cyclophosphamide has been associated with transitional cell carcinoma in the bladder later in life. Diagnosis is made by demonstration of plentiful red blood cells, white blood cells, and the absence of bacteria in urine. Therapy consists of discontinuation of the drug, prophylaxis of infection with antibiotics, diuresis, and antiinflammatory drugs such as prednisone. Intravesicular administration of a 1% formalin solution and dimethyl sulfoxide (DMSO) have been reported.[6]

Nephrotoxicity secondary to cisplatin use has been reported in dogs, and renal failure has been reported in cats after administration of doxorubicin.[7]

193.6 SUGGESTED FURTHER READING*

R Chun, L Garrett, DM Vail: Cancer chemotherapy. In SJ Withrow, DM Vail (Eds.): *Withrow & MacEwen's small animal clinical oncology*. ed 4, 2007, Saunders, St Louis, *A chapter that provides in-depth information on principles of chemotherapy administration, agents, dosages, and side effects*.

GC Couto: Management of complications cancer chemotherapy. In CG Couto (Ed.): *Veterinary Clinics of North America Small Animal Practice: clinical management of the cancer patient*. 1990, Saunders, Philadelphia, *A brief and concise chapter illustrating management strategies for chemotherapy toxicities*.

BDX Lascelles, GE Mauldin: Supportive care for the cancer patient. In SJ Withrow, DM Vail (Eds.): *Withrow & MacEwen's small animal clinical oncology*. ed 4, 2007, Saunders, St Louis, *A chapter that outlines the physiologic changes that can occur in the cancer patient and provides practical management strategies for pain and nutritional therapy to ameliorate their effects*.

GK Ogilvie, AS Moore: Chemotherapy: properties, uses, and patient management. In GK Ogilvie, AS Moore (Eds.): *Feline oncology*. 2001, Veterinary Learning Systems, Trenton, *A comprehensive guide to feline oncology, a valuable asset to the practice of feline veterinary oncology*.

* See the CD-ROM for a complete list of references

194 Chapter 194 Antimicrobial use in the Critical Care Patient

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194.1 KEY POINTS

- *Staphylococcus, Enterococcus, Escherichia coli,* and *Clostridium* are examples of microbes for which emergent multidrug resistance is limiting therapeutic options.
- Factors that increase the risk of infection with a multidrug-resistant microbe include previous antimicrobial exposure, duration of hospital stay, and inappropriate dosing regimens.
- A number of techniques or policies can be implemented in the critical care environment to reduce antimicrobial resistance.
- Emergence of resistant microbes can be reduced by designing a dosing regimen to achieve the mutant prevention concentration at the site of infection.

194.2 INTRODUCTION

Antimicrobials are among the most common with most important drugs prescribed for the critical care patient (CCP).[1] Timely, effective antimicrobial therapy is a crucial determinant of outcome in the CCP[2]; however, the advent of antimicrobial resistance has profoundly altered its use. The goal of antimicrobial therapy includes the safe eradication of infection while minimizing the advent of resistance.

The CCP is particularly at risk for infections with antimicrobial resistant bacteria. The risk of infection increases because of bacterial translocation from the gastrointestinal (GI) tract, the use of invasive procedures, and foreign surfaces conducive to bacterial colonization (e.g., catheters). Patients are often immunocompromised. Cardiovascular, renal, and hepatic dysfunction or responses alter all aspects of drug disposition, increasing the risk of either adverse drug events or therapeutic failure. Polypharmacy, or the use of multiple medications in an individual patient, increases the risk of adverse drug events and drug interactions. Finally, the sense of urgency accompanying therapeutic decision making generally leads to empiric antimicrobial use.

The principles guiding antimicrobial therapy are regularly reviewed.[3] This chapter summarizes those principles, with a focus on their relevance to the CCP. Included is a description of antimicrobial resistance, including factors predisposing to its emergence, methods by which resistance might be avoided, and then a step-wise decision path that might be implemented as antimicrobial therapy is considered in the CCP. The Infectious Diseases Society of America (http://www.idsociety.org) offers guidelines for the use of antimicrobial agents, many of which are specific to conditions characterized as critical. These guidelines are reassessed and modified on a cyclical basis.

194.3 ANTIMICROBIAL RESISTANCE

194.3.1 Advent of Resistance

Previous antimicrobial exposure is among the most predictive factors for the development of antimicrobial resistance. The diversity of the GI flora includes *E. coli* as the major gram-negative and *Enterococcus* spp as the major gram-positive aerobes; however, the often-underestimated anaerobic flora predominates. These microbes maintain an ecologic niche by competing for nutrients and actively suppressing surrounding growth through secretion of antibiotics. Self-destruction does not occur because genes encoding antibiotic secretion generally accompany genes that impart resistance. Constant exposure to antibiotics also causes surrounding commensal organisms to be primed for resistance. Rapid microbial turnover ensures frequent DNA replication and thus the potential for mutation. Genes imparting resistance are shared among organisms via integrins, plasmids, and transposons that facilitate rapid transfer of multidrug resistance.[4] Resistance to any antimicrobial drug should be anticipated when the population of bacteria reaches or exceeds 10^6 to 10^8 colony-forming units (CFU).[5]

The use of broad-spectrum antimicrobial drugs facilitates selection of resistant organisms,[6] although the potential for resistance varies among organisms. More problematic organisms have emerged since the 1990s including, in order of appearance, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), fluoroquinolone-resistant *Pseudomonas* (FQRP) and, most recently, vancomycin-resistant *Staphylococcus aureus* (VRSA). Each has developed multidrug resistance, defined as resistance to three or more antimicrobial agents to which the organism is generally considered susceptible. *Staphylococcus* is particularly intrinsically virulent, able to adapt to many different environmental conditions, and is increasingly associated with life-threatening infections. Resistance to methicillin is at a high level, reflecting a gene coding for an altered penicillin-binding protein with a low affinity for all β-lactam antibiotics, including cephalosporins and carbapenems. The advent of MRSA can be associated with cephalosporin use.[7] The gene imparting methicillin resistance has been detected in *Staphylococcus*-infected dogs.[8,9]

Escherichia coli is also emerging as a multidrug-resistant (MDR) organism, with resistance associated with fluoroquinolone treatment.[2] Even a single dose of a fluoroquinolone has been associated with changes in the resistance pattern of commensal coliforms in humans.[10] Fluoroquinolone-resistant *E. coli* has been documented in the urinary tract of dogs and other tissues[11] and has been associated with nosocomial infections in a veterinary 821
teaching hospital.[12] *E. coli* is among the isolates that are able to produce extended-spectrum β-lactamases 822
(ESBLs).

These enzymes, encoded by large plasmids, have emerged in concert with high-level use of cefotaxime and ceftazidime. They cause MDR coliforms and require special testing procedures for detection. The ESBLs are found most commonly in *Klebsiella* spp, *E. coli,* or *Proteus mirabilis* (3.1% to 9.5%), but they also have been detected in other members of the Enterobacteriaceae family and in *Pseudomonas aeruginosa*. The genetic information for ESBL is conferred between and within organisms. Newer cephalosporins are affected, including cefotaxime, ceftazidime, and ceftriaxone, as well as cefpodoxime[13] and several fourth-generation drugs. The effect on cephamycins (e.g., cefoxitin, cefotetan) is less clear. Monobactams (i.e., aztreonam), but not carbapenems (e.g., imipenem or meropenem), also are targeted by ESBLs. The impact on clavulanic acid and sulbactam is not clear, although their use in place of cephalosporins appears to reduce the emergence of ESBLs and may reduce resistance in other pathogens such as *Clostridium difficile* and VRE.[14] Decreased cephalosporin usage reduces the advent of ESBLs. Emergence of an ESBL in a patient may depend on the size of the inoculum, and detection requires special testing procedures generally not offered by diagnostic microbiology laboratories. An ESBL should be suspected with organisms resistant to cefotaxime but susceptible to β-lactam/β-lactamase combinations.

194.3.2 Nosocomial Infections

Nosocomial infections occur as a result of medical treatment, usually in a hospital or clinic setting. Nosocomial infections are formally defined as infections arising more than 48 hours after hospital admission. Nosocomial organisms are generally opportunists. The most important source probably is the environment, although transfer from caregivers or other patients is possible. The risk of nosocomial infection is 5- to 10-fold higher in the human critical care ward compared with the hospital-at-large population.[1]

Bacterial colonization by nosocomial isolates occurs in the upper respiratory tract, GI tract, and urogenital tract and on skin of hospitalized patients within a few days of hospitalization. Accordingly, nosocomial infections most commonly occur in the respiratory system or urinary tract or skin. Infection is frequently associated with invasive procedures. Nosocomial infection in veterinary CCPs has been reviewed.[15] The organisms reportedly associated with these infections in dogs and cats have been many and diverse, varying with the report. Organisms include, but not exclusively, *Serratia* spp, *Staphylococcus* spp, *Streptococcus* spp, *Klebsiella* spp, *Enterococcus* spp, and *E. coli*. As in humans, predisposing factors have included presence of indwelling catheters[16] and previous antimicrobial therapy.

Nosocomial organisms are generally characterized by complex resistance patterns; in some intensive care units (ICUs) that treat humans selected isolates are characterized by a resistance prevalence of 86%. Resistance results increased morbidity and mortality, and increased costs. Effective treatment generally requires more expensive and potentially toxic drugs; selection should be based on culture and susceptibility testing.[17]

194.3.3 Reducing Environmental Microbial Resistance

ICUs have implemented a number of techniques intended to reduce antimicrobial resistance. Each proposed or implemented strategy has theoretic benefits and limitations, but good data on their efficacy in controlling antimicrobial resistance are limited.[18,19] Hospital strategies involve a multitiered approach.

194.3.3.1 Primary Prevention

Primary prevention is accomplished by decreasing length of hospital stays, using fewer invasive devices, and placement of catheters or invasive devices by individuals educated and trained in proper (aseptic) placement (chlorhexidine is the preferred antiseptic).

194.3.3.2 Improving Infection Control

Improving infection control includes using selective decontamination procedures, preventing horizontal transmission via handwashing, glove, and gown use, using effective alternatives to soap, and improving the workload of and facilities for health care workers. New approaches include innovative catheter designs, including silver or antimicrobial impregnation. Overcrowding in the ward should be prevented. The importance of hand cleansing between patient contacts as a means to prevent transmission of infections cannot be overemphasized. Soap and water should be used first in the presence of soiling, and alcohol hand rubs can be used if soiling is not present.[6] Selective GI decontamination to prevent antimicrobial infection is controversial.[6] Strategies that decrease patient exposure to antimicrobial agents are preferred to decontamination.

194.3.3.3

Education

Education of hospital personnel, including staff and clinicians concerning the existence, causes, and need for reduction of antimicrobial resistance is imperative.[6]

194.3.3.4

Changing Antimicrobial Prescribing Behaviors

Antimicrobial drug prescribing behaviors are the most significant mechanism by which bacterial resistance is likely to be reduced in the critical care environment.[20] Protocols should be designed and subsequently implemented with the intent to deescalate antimicrobial use. Deescalation is among the more rational paradigms for empiric antimicrobial use in hospitalized patients with serious bacterial infections.[20] The goal of deescalation is to prescribe an initial antibacterial regimen that will cover the most likely bacterial pathogens associated with infection, thus balancing the need for appropriate therapy, while minimizing the risk of emerging antibacterial resistance.[20] The three-pronged approach includes narrowing the antibacterial regimen through culture, assessing the susceptibility for dosage determination, and choosing the shortest course of therapy clinically acceptable.

Although preapproval of selected drug use (e.g., by a committee) and antibiotic restriction practices may be useful, recommended and more reasonable deescalation procedures include rotating the use of antimicrobial drugs on a regular schedule, and designing the dosing regimen such that therapeutic success is maximized, resistance is minimized, and duration of therapy can be reduced.[18] Deescalation procedures in humans have been associated with a return to susceptibility for ceftazidime, piperacillin, imipenem, and fluoroquinolones.

The risk of antimicrobial resistance is associated with both dose and duration of therapy. Basing drug selection on culture and susceptibility information, with accompanying minimum inhibitory concentration (MIC) data, 822
is critical both to identify current bacterial resistance in patients at risk and to best design an individual patient 823
dosing regimen. Approaches to dosage adjustment are discussed next. However, increasingly in human medicine, dosages are being based on the mutant prevention concentration (MPC) rather than the MIC.[5]

The MPC is defined as the highest MIC identified in a patient population of susceptible isolates ($\geq 10^7$) of an organism, thus including those CFUs or isolates that have undergone the first-step mutation. The MIC obtained from culture and susceptibility testing most likely reflects the majority of CFUs causing infection in the patient. However, the MIC is less likely to reflect those CFUs that already have undergone the first-step mutation (i.e., are characterized by higher MIC). Should drug therapy target the MIC, competing isolates will be inhibited or killed, allowing the mutants to emerge. In healthy patients, this population can probably be controlled by host defenses. However, in less capable patients, the new emergent population will be characterized by a higher MIC that is potentially unattainable with a safe dosing regimen.

Unfortunately, determining the MPC of an isolate cultured from a patient requires culture based on 10^7 or more organisms; current techniques cannot achieve this large an inoculum. Experimentally, the ratio of MPC to MIC for various fluoroquinolones given for infection by human pathogens ranges from a low of 6 to 10 for *E. coli* but 23 to 50 (and as high as 125) for selected drugs given for infection by *Staphylococcus aureus*.

Rational combination antimicrobial therapy can be a powerful tool for enhancing efficacy while reducing resistance in the CCP. Combination therapy should be considered routinely for organisms often associated with MDR (e.g., *P. aeruginosa, Enterococcus* spp, and MRSA). Resistance to a combination of antimicrobial drugs should be anticipated when the population reaches 10^{14} or more CFUs. Drugs chosen for combination therapy should be selected rationally, based on target organisms. Mechanisms of action should complement, rather than antagonize, one another.[21]

In general, "bacteriostatic" drugs that inhibit ribosomes and thus microbial growth (e.g., chloramphenicol, tetracyclines, and erythromycin) should not be combined with drugs whose mechanism of action depends on protein synthesis, such as growth of the organism (e.g., β-lactams) or formation of a target protein. The bactericidal activity of β-lactams and fluoroquinolones depend on continued synthesis of bacterial proteins. Antagonistic effects have been well documented between β-lactam antimicrobials and inhibitors of ribosomal activity.[21]

Chemical antagonism is also possible among two or more antimicrobials; the prototypical example is chemical inactivation of aminoglycosides and quinolones by β-lactams. However, chemical antagonism is unlikely to occur at concentrations achieved systemically in the clinical patient. In contrast to antagonism, drugs that have the same mechanism of action may act in an additive or synergistic fashion. The prototypical example of synergism is the combination of β-lactams and aminoglycosides; aminoglycoside penetration is facilitated by penicillin-induced cell wall failure.[21] Indeed, aminoglycoside activity against *Enterococcus* spp is adequate only when the agent is used synergistically with a cell wall–active antibiotic, such as a β-lactam or vancomycin. Synergism has also been demonstrated against some strains of *Enterobacteriaceae,* P. aeruginosa, staphylococci (including MRSA), and other microorganisms. Enhanced movement into the bacteria may occur with other drugs (e.g., potentiated sulfonamides, fluoroquinolones) when combined with a β-lactam.

Combination antimicrobial therapy may be selected for a polymicrobial infection. Aminoglycosides or fluoroquinolones are often combined with β-lactams, metronidazole, or clindamycin to target both aerobic gram-positive and gram-negative infections, or aerobic infections caused by both aerobes and anaerobes. The combined use of selected antibiotics may result in effective therapy against a given microbe, even when either drug alone would be ineffective.

194.4 ANTIMICROBIAL SELECTION

The following approach is recommended whenever antimicrobial therapy is being considered in the CCP.

194.4.1 Critique the Need for Antimicrobial Therapy

Perhaps more so than in other patients, the need for prophylactic or treatment is a necessary consideration in the CCP. The sense of urgency, the need to cover all bases in the face of unclear diagnostics, and standards of care that include "routine" use of drugs all lend themselves to empiric antimicrobial therapy. Few studies have demonstrated appropriate timing of antimicrobial therapy. In humans, up to 53% of hospitalized patients receive antibiotics,[6] with between 14% and 43% deemed unnecessary.[22] Statistics are not available for veterinary patients but are probably similar.

The advent of a fever should not always be assumed to reflect infection; guidelines have been offered by the Infectious Diseases Society of America.[23] An exception might exist for neutropenic patients for whom fever cannot otherwise be explained.[24] Culture results do not necessarily confirm infection, because they may not discriminate between normal, commensal flora and opportunistic, pathogenic isolates. Vibrant and pure growth supports, but does not confirm, a cultured organism as the infecting isolate. Gram staining of cytologic samples with evidence of phagocytized organisms is an often forgotten, but potentially pivotal, guide for initial selection of antimicrobial therapy. Empiric selection is more directed at nosocomial infections, although confirmation should be based on culture results.

The number of isolates considered necessary for diagnosing definitive infection varies with the tissue, but for the urinary tract generally is considered to be 10^5 CFU or more versus 10^3 CFU or more for the respiratory tract. The conundrum facing the critical care specialist is that little information exists to help confirm evidence of infection, yet empiric use is likely to contribute to resistance. This situation is likely to persist until molecular diagnostic techniques catch up with diagnostic needs. To prevent adding injury to insult, once the decision is made to treat with antimicrobials, all subsequent decisions should be oriented toward both ensuring therapeutic efficacy and reducing the risk of resistance.

194.4.2 Identify the Target and Its Susceptibility

Initial empiric therapy should be accompanied by properly collected culture samples with the drug and dosing regimen based on susceptibility testing.[3] The complex nature of nosocomial organisms mandates that they also be cultured.[17] The use of broad-spectrum drugs increases the risk of resistance. Although by its nature empiric drug selection is broad, an attempt should be made to narrow the spectrum of the chosen drug. Empiric selection should be based on appropriate evidence provided in the literature, hospital susceptibility data, and the relevant medical history of the patient, including site and cause of assumed infection, and previous antimicrobial therapy.

Historical data reported in the literature may be useful in identifying the most likely infecting organisms in sample populations of animals, but they have often failed to discriminate commensal versus pathogenic (causing harm to the patient) isolates. Incorrect choices have been documented in close to 50% of patients in shock. For critically ill patients, organisms generally represent the normal flora of the alimentary canal or nosocomial organisms. The source of infection may help narrow the spectrum of empiric therapy if selected organisms are more likely to infect some body systems more than others. For example, genitourinary tracts often are infected with gram-negative aerobes, whereas abdominal infections generally are caused by gram-negative aerobes initially, followed by anaerobes.

Anaerobic coverage should also be considered for selected infections (e.g., osteomyelitis) or those involving deep, isolated areas or hollow organs or those associated with a foul smell and marked inflammation, including abscess formation. Granulocytopenic or otherwise immunoincompetent patients are more likely to be infected by aerobic gram-negative organisms. Previous antimicrobial use (the author recommends within the past 3 months) should be assumed to have selected for resistant organisms in the patient and thus, should influence drug selection. Use of β-lactams is likely to have resulted in resistance toward other β-lactams, whereas previous use of fluorinated quinolones is more likely to be associated with MDR bacteria (unpublished data, author).

Identification of the target microbe is not enough. The target must also be assessed for relative susceptibility to the drug of interest. Tube dilution rather than agar gel diffusion methods are preferred for the quantitative information that they provide.[3] If an isolate is not yet identified, sample population data should be considered.

Organism susceptibility statistics, should be generated on an annual basis for each hospital, and such data should help govern the selection of empiric therapy. Comparison of sample population MIC_{90} of organisms cultured from previous patients in the hospital or from the literature[3,11] to the breakpoint MIC or peak plasma drug concentration (C_{max}) of the drug obtained with the recommended dosage can provide insight into relative susceptibility, as well as the design of a regimen (see later discussion).

194.4.3 Identify the Site of Infection

Three levels of drug penetration exist in normal tissues. Sinusoidal capillaries, found primarily in the adrenal cortex, pituitary gland, liver, and spleen, present essentially no barrier to bound or unbound drug movement. Fenestrated capillaries such as those located in kidneys and endocrine glands contain pores that do not present a barrier to unbound drug, and movement is thus facilitated between the plasma and interstitium.[25] However, culture and susceptibility testing is based on a MIC determined in vitro in the absence of protein. Therefore the MIC overestimates active concentrations of drugs bound in vivo to proteins (e.g., doxycycline, cefazolin). Continuous capillaries, such as those found in the brain, cerebrospinal fluid, testes, prostate, muscle, and adipose tissue, present a barrier of endothelial cells with tight junctions that precludes drug movement. For infections in tissues with nonfenestrated capillaries, the dosing regimen of water-soluble drugs (e.g., β-lactams and aminoglycosides, selected sulfonamides and selected tetracyclines) should be adjusted for potentially poor drug distribution to the site of infection. Indeed, dosages for β-lactams are often adjusted up to 10-fold in treating human central nervous system infections.

The volume of distribution of a drug indicates the likelihood of tissue penetration, although it cannot indicate to which tissues the drug will be distributed. Distribution of water-soluble drugs tends to be limited to the extracellular fluid compartment, resulting in a volume of distribution approximating extracellular fluid (i.e., 0.2 to 0.3 L/kg).[26] In contrast, a lipid-soluble drug that can penetrate cell membranes will be distributed to a volume approximating that of total body water (i.e., ≥0.6 L/kg).

Accumulation of a drug in selected tissues can facilitate successful therapy and reduce the development of resistance. Phagocyte accumulation of selected drugs (e.g., fluoroquinolones, macrolides, selected lincosamides) up to several hundred–fold higher than in plasma may facilitate treatment of intracellular infections (e.g., *Brucella* spp, cell wall–deficient organisms, intracellular parasites, and facultative intracellular organisms such as *Staphylococcus*).[27-29] Furthermore, accumulated drug released by dying phagocytes at the site of infection will increase concentrations to which the infecting microbe is exposed. Although renally excreted drug will accumulate in urine and biliary excreted drug in the bile, these high concentrations may occur only in the fluid and not in surrounding tissues; therefore caution must be used when dosing regimens are designed. However, culture and susceptibility testing will underestimate efficacy of drugs that can be applied topically at the site of infection. In such situations, several thousand–fold of the MIC may be reached. On the other hand, topical application of antimicrobial drugs in the CCP is not common. An example might include aerosolization, but limited aerosol penetrability and potential side effects of aerosolized particles preclude aerosolization as the sole method of drug administration for respiratory tract infections.

194.4.4 Minimize the Impact of Microbial Factors

In addition to the development of resistance, microbes can negatively affect antimicrobial therapy. One mechanism is the adverse impact that the microbe imparts to the host's response to infection. Materials released from microbes facilitate invasion, impair cellular phagocytosis, and damage host tissues. The “inoculum effect” of ESBLs results in cephalosporin resistance with a larger (10^7) compared to smaller (10^5) inoculum.

Infection in epithelial tissues (i.e., uroepithelium and respiratory epithelium) is facilitated by bacterial adherence. Materials secreted by organisms often contribute to the marked inflammatory host response and clinical signs of infection. Soluble mediators released by organisms (hemolysin, epidermolytic toxin, leukocidin) may damage host tissues or alter host response. Staphylococci produce slime, *Nocardia* spp produce calcium-containing “sulfur granules,” and *Pseudomonas* and other gram-negative organisms produce glycocalyx, or biofilm.

Biofilm consists of microcolonies of pathogenic and host microbes embedded in a polysaccharide that is produced by the bacteria. Translocation of the normal microflora in the biofilm to otherwise sterile tissues (which can be facilitated by foreign bodies) may lead to acute infections (again, associated with biofilm) and the accompanying inflammatory response. Persistent, chronic bacterial infections may reflect biofilm-producing bacteria; persistent inflammation associated with immune complexes contributes to the clinical signs. Unfortunately, bacteria growing in biofilms resist antimicrobial killing and immune defenses of the host more easily. Biofilm can facilitate organism growth in foreign bodies in the host, including catheters. The nidus of bacteria may ultimately cause infection, as was demonstrated in dogs undergoing experimental catheterization of the portal vein.[30] However, organism growth in catheters does not necessarily lead to infection, and isolates cultured from urinary catheter tips are not necessarily those causing urinary tract infection.[31]

194.4.5

Delineate Host Factors That Will Complicate Therapy

Careful consideration must be given to host factors that can reduce concentrations of active drug at the site of infection.

194.4.5.1

Changes in Drug Disposition

Pathophysiologic changes associated with the critical nature of patient illness have an impact on each drug's disposition, including absorption, distribution, metabolism, and excretion. Either the dose or dosing interval must be adjusted accordingly. Drug concentrations are most likely to be affected by changes in absorption and distribution, whereas changes in distribution, metabolism, and excretion can alter the elimination half-life and thus the dosing interval. Fortunately, changes in absorption no longer require consideration with intravenous administration in critically ill patients. However, for subcutaneous or intramuscular drug administration, changes in blood flow in the CCP may slow the rate of absorption. Distribution will similarly be affected by changes in perfusion, particularly in the patient in cardiovascular shock; volume replacement may correct some of these changes.

Changes in drug concentration are influenced by the changes in the volume to which the drug is distributed. An increase in the volume of distribution decreases plasma drug concentration and vice versa. However, the clinical impact differs with the lipophilicity of the drug. For water-soluble drugs (aminoglycosides, β-lactams and glycopeptides), the volume of distribution can be increased by the accumulation of fluids in peripheral tissues, including the pleural space and peritoneal cavity.[1] Septic shock and trauma are the two most common causes of volume of distribution expansion in the CCP.[1] Aggressive fluid therapy may also decrease drug concentrations.

Each of the foregoing examples will decrease tissue antimicrobial exposure. Several studies have associated therapeutic failure of aminoglycosides with decreased plasma drug concentrations in septic patients.[1] Dosages should be increased proportionately in these situations. Monitoring of peak concentrations (1.5 to 2 hours after administration) might be considered for patients receiving aminoglycosides to ensure that therapeutic concentrations are being achieved at the chosen dosage. Although volume contraction associated with dehydration may cause the opposite effect (higher plasma drug concentrations), volume repletion rather than dosage modification should be implemented.

Interestingly, hypoalbuminemia also contributes to decreased antimicrobial exposure, even for drugs that traditionally are not bound significantly, probably due to peripheral fluid retention. In general, dosage increases of 1.5-fold to 2-fold are indicated.[1] For lipid-soluble drugs, the impact of disease-induced changes in distribution volume should be negligible if the dosage is calculated on a mg/kg basis. However, this assumes that dosing is based on an accurate weight, which may change as intravascular and interstitial volumes are replaced.

Changes in drug elimination, expressed as changes in elimination half-life, accompany changes in both clearance (inversely proportional) and volume of distribution (directly proportional). In general, critical illness decreases drug clearance, although an exception is patients in the hyperdynamic state of septic shock (frequently associated with increased clearance). The impact on clearance, as with volume of distribution, also varies with lipophilicity.

Water-soluble drugs are generally excreted renally. Changes in glomerular filtration will be associated with proportional changes in renal clearance of drugs. Lipophilic drugs are typically metabolized by the liver before renal and, less commonly, biliary excretion occurs. Excretion of these drugs may be decreased in animals with hepatic disease, although the degree of hepatic dysfunction generally must be profound (i.e., altered albumin concentration) before drug metabolism is affected.

In general, decreased clearance causes a proportional decrease in elimination half-life and thus a prolongation of dosing interval, or a decreased rate of constant infusion for potentially toxic drugs. For increased clearance, dosing intervals may need to be shortened for time-dependent drugs (see “Designing the Dose Regimen” later in this chapter). It is important to remember that clearance and volume of distribution have opposite and equal effects on the elimination half-life. Further, predicting the proper dosing regimen is complicated by the complex pathophysiology of critical diseases. For example, increased clearance associated with the hyperdynamic state of septic shock may be balanced by decreased renal function. In patients that are dehydrated, decreased clearance may be balanced by a decreased volume of distribution such that elimination half-life may not change despite marked changes in both parameters. However, once the volume is replaced, the elimination half-life may be prolonged.

194.4.5.2

Host Immune Response

On the one hand, immunocompromise increases the risk of infection, mandating the need for achievement of bactericidal concentrations of drug at the site of infection. On the other hand, too much of a good thing (inflammatory response) can also lead to therapeutic failure. Bactericidal concentrations are paramount to therapeutic success in immunocompromised hosts (e.g., viral infections, granulopoietic patients, those receiving immunoinhibiting drugs) or immunocompromised sites (septicemia, meningitis, valvular endocarditis, and osteomyelitis). However, classification of bactericidal versus bacteriostatic actions is based on in vitro methods, and the minimum bactericidal concentration of bactericidal drugs may not be achievable at the site of infection in the patient. Dosing regimens should be designed to ensure bactericidal concentrations are reached when possible. Occasionally, bactericidal concentrations of a bacteriostatic drug can be achieved in some tissues (e.g., if the drug accumulates at the site of infection).

Host inflammatory response can profoundly alter drug efficacy. Although acute inflammation may initially increase drug delivery to and drug concentration at the site of infection, a marked inflammatory response or chronic inflammation may result in the opposite effect. Purulent exudates present an acidic, hyperosmolar, and hypoxic environment that impairs the efficacy of many antimicrobial agents. Hemoglobin and degradative products of inflammation can bind them. Selected drugs, including aminoglycosides (and probably highly protein-bound drugs), are bound to, and thus inactivated by, proteinaceous debris that accumulates secondary to inflammation.

Aminoglycosides (which require active transport into the microbe) may be ineffective in an anaerobic environment. Some antimicrobial drugs can inhibit neutrophil function. Accumulation of cellular debris associated with the inflammatory process can present a barrier to passive antibiotic distribution. Deposition of fibrous tissue at the infected site further impairs drug penetrance and distribution.

194.4.5.3

Host Toxicity

Host (patient) cells are eukaryotic; but bacterial targets are prokaryotic and, as such, targets of antibacterial therapy are sufficiently different from mammalian cells that, as a class, many antibacterial agents are safe. Exceptions do occur if the microbial target occurs in mammalian cells and is structurally similar to them. Accordingly, drugs that target cell membranes, such as colistin and polymyxin, predictably cause sufficient nephrotoxicity that antimicrobial use is generally limited to the topical route of administration.

Other toxicities associated with antimicrobial drugs tend to reflect actions unique from their antibacterial effects. Aminoglycosides remain the most effective drugs for treatment of gram-negative infections, but they are predictably nephrotoxic. Toxicity is related to the duration of exposure. Accordingly, kidneys must be allowed sufficient time to eliminate accumulated drug such that trough plasma drug concentrations (PDCs) drop below a threshold, generally less than 1 to 2 μg/ml.[32] Toxicity is further minimized by ensuring hydration with sodium-containing fluids, once-daily therapy, a high dosage such that duration of therapy is minimized,[33] administration in the morning (diurnal animals), and the avoidance of nephroactive drugs (e.g., nonsteroidal antiinflammatory drugs, angiotensin enzyme inhibitors, diuretics). Fluoroquinolone-induced retinal degeneration in cats limits their general use to 5 mg/kg q24h,[34] which is probably a dosage conducive to resistance.[3,11] Geriatric cats and cats with renal disease may be predisposed to retinal toxicity. An anaphylactoid reaction to enrofloxacin caused by direct mast cell degranulation may be minimized by rapid administration. *Staphylococcus pyogenes* in humans and *Streptococcus canis* in animals have been associated with streptococcal toxic shock syndrome and necrotizing fasciitis associated with fluoroquinolone use.[35,36]

Release of endotoxin by dying microbes can lead to therapeutic failure despite successful eradication of infection. The amount released varies among, and within, the antimicrobial classes, perhaps reflecting the drug's mechanism of action. Aminoglycosides have been associated with the least and β-lactams the most endotoxin release. A notable exception to β-lactams occurs with the carbapenems (e.g., imipenem or meropenem), which are associated with the least endotoxin release.[37] The varying amounts of endotoxin released from bacteria in response to β-lactams may reflect different affinities of the drugs for different penicillin-binding proteins. Selected third-generation cephalosporins also appear to be associated with less endotoxin release. The reported release of endotoxin associated with quinolones is variable, depending on the study; quinolones, as with low (nonantimicrobial) dosages of polymyxins, may reduce endotoxin sequelae by binding the toxin.

194.4.6 Designing the Dosing Regimen

Clearly, the closer the MIC of the infecting isolate is to the breakpoint MIC of the drug, or the maximum drug concentration achieved at recommended dosages, the more important it is that appropriate modifications be made to the recommended dosing regimen.[3] The relationship between MIC and the magnitude and time course of PDC allows drugs to be categorized as either time-dependent or concentration-dependent (sometimes referred to as *dosage-dependent*).

Time-dependent drugs are exemplified by β-lactams, whose presence is necessary as long as the isolate is building new cell walls. Thus efficacy is best predicted by the percentage of time (T) that the PDC is above the MIC (or T > MIC), which ideally is at least 50% of the dosing interval.[38,39] Increasing the frequency of dosing is likely to be more cost effective than increasing the dosage. For example, a dosage of 20 mg/kg of amoxicillin achieves approximately 13 μg/ml in the plasma and the drug elimination half-life is approximately 1.2 hours. If the MIC of the infecting microbe is 4 μg/ml, the PDC will decline such that the MIC is reached in less than 3 half-lives, or approximately 4 hours. This would allow an 8-hour dosing interval. Doubling the dosage of the drug adds 2.4 hours (twice the half-life if 50% of the dosing interval is to be covered), but it will have to be quadrupled to allow a 12-hour dosing interval. This assumes that drug concentrations achieved in the plasma are also achieved in tissues and targets the minimum 50% period.

Constant rate infusions (CRIs)[40] might be ideal for time-dependent drugs as was demonstrated in an in vitro model of ceftazidime CRI for treatment of *P. aeruginosa* infection.[41] Slow-release products whose drug release is sufficiently fast to allow C_{max} to surpass the MIC also might be more effective than intermittent administration.[42] Drugs with a long half-life, such as cefpodoxime, also are appealing because they allow for a convenient dosing interval as long as the organism MIC is sufficiently distant from peak plasma drug concentrations.

Finally, efficacy should also be enhanced for time-dependent drugs that accumulate in the active (unbound) form in tissues (i.e., macrolides[43]) or drugs that accumulate in phagocytes. Some drugs (e.g., macrolides) are characterized by time dependency for some organisms but concentration dependency for others.

Concentration-dependent drugs, best represented by the fluoroquinolones and aminoglycosides (both of which irreversibly bind to their targets), are characterized by efficacy that is predicted by the C_{max} compared with the MIC of the infecting organism.[3,39] For such drugs, the magnitude of the C_{max}/MIC generally should be a minimum of 10 to 12 and greater for more difficult infections (e.g., *P. aeruginosa* or infections caused by multiple organisms).[44,45] More recently, efficacy of concentration-dependent drugs is best predicted by the area under the curve (AUIC), the ratio of AUC (area under the curve for 24 hours, which is influenced by both dose and interval) to MIC. An AUIC of over 125 is generally associated with bacterial killing and decreased resistance. Thus for treatment of some infections, the dosing regimen might be designed to maximize both the C_{max}/MIC and the AUC/MIC (i.e., a higher dosage, targeting a higher C_{max}/MIC, and a shorter dosing interval, targeting a higher AUC/MIC). Concentration-dependent drugs in particular exhibit a postantibiotic effect, which describes the phenomenon of prolonged antimicrobial effects after brief exposure to the drug.[46]

Design of the dosing regimen also includes consideration of the duration of therapy. In humans, discontinuing unnecessary antimicrobial therapy has been associated with a decrease in hospital stay, cost, antimicrobial resistance, and suprainfection.[6] Short courses (i.e., 3 to 5 days) of intensive therapy are increasingly accepted in lieu of the traditional 7 to 10 days of therapy.

194.5 SUGGESTED FURTHER READING*

DM Boothe: Principles of antimicrobial therapy. *Vet Clin North Am Small Anim Pract*. **36**, 2006, 1003, *An article that addresses more in-depth approaches through which antimicrobial therapy may be rationally applied to the individual patient such that resistance might be minimized without compromising patient response*.

DI Hsu, MP Okamoto, R Murther: Fluoroquinolone-resistant *Pseudomonas aeruginosa:* risk factors for acquisition and impact on outcomes. *J Antimicrob Chemother*. **55**, 2005, 535, *Risk factors for the development of fluoroquinolone resistance in humans included fluoroquinolone exposure, nosocomial infections, and diabetes mellitus. Fluoroquinolone-resistant cases experienced delays before receiving effective therapy and also had poorer outcomes*.

WT Hughes, D Armstrong, GP Bodey, et al.: 1997 Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis*. **25**, 1997, 551, http://www.idsociety.org, . Accessed June 4, 2007 *General guidelines for the empiric treatment of neutropenic human patients. Website has updated information*.

JA Johnson: Nosocomial infections. *Vet Clin North Am Small Anim Pract*. **32**, 2002, 1101, *A review and discussion of nosocomial infections and their importance in small animal medicine*.

N Lee, KY Yuen, CR Kumana: Clinical role of β-lactam/β-lactamase inhibitor combinations. *Drugs*. **63**, 2003, 1511, *A review of the use of β-lactam plus lactamase inhibitor combination therapy for the treatment of a wide variety of infections and MDR bacteria*.

RC Li, ZY Zhu: The integration of four major determinants of antibiotic action: bactericidal activity, postantibiotic effect, susceptibility, and pharmacokinetics. *J Chemother*. **14**, 2002, 579, *A review of the advantages of using the mentioned four factors to prescribe antibiotics in a fashion that would effectively treat the cultured organism(s) while minimizing the development of bacterial resistance*.

M Schwaber, SE Cosgrove, H Gold, et al.: Fluoroquinolones protective against cephalosporin resistance in gram-negative nosocomial pathogens. *Emerg Infect Dis*. **10**, 2004, 94, http://www.cdc.gov/eid, . Accessed June 4, 2007 *Study that examined 282 cases with a resistant gram-negative pathogen and found that risk factors for resistant nosocomial organisms included surgery, intensive care unit stay, and receipt of a β-lactam/β-lactamase inhibitor, a ureidopenicillin, or a third-generation cephalosporin*.

RS Slavik, PJ Jewesson: Selecting antibacterials for outpatient parenteral antimicrobial therapy: pharmacokinetic-pharmacodynamic considerations. *Clin Pharmacokinet*. **42**, 2003, 793, *Reviews the pertinent pharmacokinetic-pharmacodynamic considerations that should be taken into account when prescribing antimicrobial therapy for outpatients*.

SD Smarick, SC Haskins, J Aldrich, et al.: Incidence of catheter-associated urinary tract infection among dogs in a small animal intensive care unit. *J Am Vet Med Assoc*. **224**, 2004, 1936, *Article that discusses risk factors of catheter-associated urinary tract infection in dogs and specifically addresses bacterial culture of urine samples versus that of catheter tips*.

E Sturenburg, D Mack: Extended spectrum β-lactamases: implications for the clinical microbiology laboratory, therapy and infection control. *J Infect*. **47**, 2003, 273, *Paper that aims to increase awareness and understanding of the growing resistance patterns of bacteria, specifically the ESBL organisms*.

PL Toutain, JR del Castillo, A Bousquet-Melou: The pharmacokinetic-pharmacodynamic approach to a rational dosage regimen for antibiotics. *Res Vet Sci*. **73**, 2002, 105, *Pharmacokinetic-pharmacodynamic surrogate indices (AUIC, AUC/MIC,* C_{max}*/MIC, T greater than MIC) for measuring antibiotic efficacy are reviewed and discussed, with specific relevance to various types of antibiotics*.

* See the CD-ROM for a complete list of references

195 Chapter 195 Penicillins and Cephalosporins

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195.1 KEY POINTS

- Penicillins and cephalosporins vary widely in their spectrum of activity.
- Resistance to penicillins and cephalosporins is a growing concern.
- Methicillin-resistant *Staphylococcus aureus* is resistant to all β-lactam antibiotics.

195.2 INTRODUCTION

Fleming's observation in 1929 that colonies of staphylococci lysed on a petri dish contaminated with the *Penicillium* mold ushered in the era of modern antimicrobial therapy. His initial efforts to extract the bactericidal substance failed, and it was 11 years before Chain and Florey succeeded in purifying large quantities of the first penicillins from *Penicillium notatum*. By the end of the decade penicillin G was in widespread clinical use. Limitations to penicillin G's efficacy were noticed almost immediately. These included poor oral bioavailability, rapid development of resistance due to the presence of β-lactamase, and poor activity against gram-negative organisms. Development of the cephalosporins overcame many of these limitations.

The penicillins, cephalosporins, and carbapenems are referred to as *β-lactam antibiotics*. All members of this class share a basic structure, the presence of a β-lactam ring. The β-lactam ring is essential for the biologic activity of these drugs. Substitutions can be made on the β-lactam ring for specific purposes such as increasing β-lactamase resistance, enhanced efficacy against specific pathogens, and altering pharmacokinetic properties.

195.3 MECHANISM OF ACTION

All β-lactam antibiotics work by interfering with bacterial cell wall synthesis. They do this by binding to and inhibiting transpeptidases and peptidoglycan-active enzymes that are collectively referred to as *penicillin binding proteins (PBPs)* that catalyze the cross-linking of the glycopeptides that form the bacterial cell wall. β-Lactams are bactericidal, but they do require actively growing cells to be efficacious.

The difference in susceptibility of gram-positive and gram-negative organisms depends upon the number and type of drug receptors, the amount of peptidoglycan present (gram-positive organisms have a much thicker cell wall), and the amount of lipid in the cell wall.[1]

195.4 PHARMACOLOGY

When administered intravenously, β-lactams are distributed widely in body fluids and tissues. They are lipid insoluble and do not enter living cells well. After oral administration, bioavailability will vary greatly among drugs depending upon their acid stability and protein binding. Ampicillin, in particular, has poor bioavailability when administered orally.[2]

Despite their wide volume of distribution, most of the β-lactams do a poor job of crossing biologic membranes, and their concentration in the eye and prostate may be only one tenth that of the serum concentration.[3] However, penicillins and cephalosporins are indicated for certain infections within the central nervous system (CNS) because bactericidal levels of drugs can be found within the CNS, benefitting those with active inflammation of the meninges.[2] Most absorbed β-lactams are excreted actively by the kidney into the urine. As a result, urine levels of β-lactams may be several-fold higher than those seen in serum.

Classically cephalosporins have been divided into three, and more recently four, generations. As a general rule cephalosporins became more gram-negative specific with increasing generations. However, the advent of newer drugs such as ceftiofur and cefpodoxime, with a spectrum of action most similar to that of first-generation cephalosporins, has made this scheme confusing. As a result, a new classification scheme consisting of seven groups has been proposed.[2] Using this scheme, drugs are divided by both their spectrum of action and whether they require parenteral or enteral administration.

195.5 RESISTANCE

195.5.1 Production of β-Lactamase

Some bacteria, such as staphylococci and most gram-negative rods, produce a β-lactamase that inactivates β-lactams by breaking their β-lactam ring. More than 60 enzymes have been described. Many of these enzymes are found on plasmids, which allows for transmission of resistance both within and between bacterial species.

195.5.2 Changes in Cell Wall Permeability

Some bacteria do not produce β-lactamase but avoid the effects of β-lactams by changing their cell wall to limit the permeability of the drug, thus preventing the drug from reaching the PBP.

195.5.3 Changes in Penicillin-binding Proteins

Some bacteria can become resistant to β-lactam antibiotics by altering their PBP. The PBP can still cross-link glycopeptides, while preventing binding of the β-lactam antibiotic. 828 829 The most important instance of this type of mutation in the acquisition by *S. aureus* of a plasmid that codes for PBP-2a. As a result of this alteration in its PBPs, *S. aureus* is resistant to all β-lactam antibiotics.

195.6 SELECTED PENICILLINS AND CEPHALOSPORINS

195.6.1 Penicillin G

In general penicillin G has a good spectrum of action against gram-positive and anaerobic infections, with the exception of some *Staphylococcus* spp. Penicillin G is synergistic with aminoglycosides, and this combination may be effective against staphylococci. Penicillin G is the drug of choice for the treatment of streptococcal infection (e.g., necrotizing fasciitis), clostridial infection, and actinomycosis.

195.6.2 Extended-Spectrum Penicillins

Both amoxicillin and ampicillin have similar spectrums of action; however, the oral bioavailability of amoxicillin is much greater, and as a general rule ampicillin should be given only parenterally. The extended-spectrum penicillins are less active against gram-positive and anaerobic infections than penicillin G, but they have a much greater efficacy against gram-negative species. Unfortunately, growing resistance is a problem and therapeutic failures are becoming more common.

Both ampicillin and amoxicillin are available in a potentiated form combined with sulbactam and clavulanic acid, respectively. The addition of a β-lactamase inhibitor results in a much greater efficacy against gram-negative organisms as well as some β-lactamase–producing gram-positive organisms.

195.6.3 Antipseudomonal Penicillins

The antipseudomonal penicillins (ticarcillin, piperacillin) exhibit a greater activity against *Pseudomonas* and *Proteus* than is seen with the other penicillins. It should be noted that the antipseudomonal penicillins exhibit poor activity against *Escherichia coli* and many other gram-negative organisms. The combination of ticarcillin with clavulanic acid does provide for greater gram-negative coverage.

195.6.4 First-Generation Cephalosporins

First-generation cephalosporins (cefazolin, cephalothin, cephalexin) have increased activity against some β-lactamase–producing organisms such as *Staphylococcus*. In general, they display a high level of activity against gram-positive organisms, moderate activity against gram-negative organisms, and minimal activity against anaerobes. Cephalothin demonstrates less gram-negative activity than cefazolin. Members of this group are used commonly as initial empiric and perioperative therapy because of their spectrum of action and safety profile.

195.6.5 Second-Generation Cephalosporins

Because of their stability against β-lactamase, second-generation cephalosporins (cefaclor, cefoxitin, cefotetan, cefuroxime) have a broad spectrum of activity. In general, they are moderately efficacious against gram-positive organisms and have a greater spectrum against gram-negative organisms than the first-generation cephalosporins.

195.6.6 Third-Generation Cephalosporins

Third-generation cephalosporins (cefotaxime, ceftriaxone, ceftiofur, cefixime, ceftazidime, cefpodoxime) vary greatly in their spectrum of action, and the efficacy of one drug in this class against an organism does not guarantee efficacy if other class members are employed. The classic third-generation cephalosporins cefotaxime, ceftriaxone, cefixime, and ceftazidime have a high degree of specificity and efficacy for gram-negative organisms. These drugs are considered the treatment of choice for empiric therapy of infections located within the CNS.

195.6.7 Carbapenems

The carbapenems (imipenem, meropenem) are the only class of antibiotics which are considered to be truly broad spectrum when employed alone. It should be noted that, as with all β-lactam antibiotics, methicillin-resistant *S. aureus* will be resistant to the carbapenems. Imipenem is combined with cilastin, which decreases the rate of renal excretion, resulting in higher plasma levels. It should also be noted that neurologic side effects, including seizures, have been noted in veterinary patients treated with imipenem. Meropenem has a lower incidence of neurologic side effects in humans. In general, carbapenems should be reserved for treating severe life-threatening infections when other options are not available.

195.7 SUGGESTED FURTHER READING*

D Boothe: In *Small animal clinical pharmacology and therapeutics*. 2001, Saunders, Philadelphia, *An excellent reference for everyday use that covers basic pharmacology and provides practical guidance for choosing appropriate antimicrobials for clinical patients*.

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* See the CD-ROM for a complete list of references

196 Chapter 196 Aminoglycosides

Reid P. Groman, DVM, DACVIM

196.1 KEY POINTS

- Despite considerable advances in the development of newer antimicrobial drugs, aminoglycosides remain important agents for treating serious infections with aerobic gram-negative and select gram-positive microorganisms.
- Aminoglycosides are known to exhibit synergistic bactericidal effects when administered in combination with β-lactam antibiotics.
- Aminoglycosides, like the fluoroquinolones, exhibit concentration-dependent killing; that is, bacterial killing is more rapid and effective when they are present at higher concentrations at the site of infection. This distinguishes the aminoglycosides from β-lactams and other commonly used antimicrobials that kill bacteria in a time-dependent fashion.
- Nephrotoxicity is the most serious side effect of aminoglycosides.
- Single daily dosing (SDD) of the aminoglycosides is possible because of their rapid concentration-dependent killing and postantibiotic effect. SDD appears to be safe and efficacious in most small animal populations.
- The role of therapeutic drug monitoring using SDD is not well defined in small animal medicine.

196.2 INTRODUCTION

Aminoglycoside antimicrobial drugs, notably gentamicin and amikacin, constitute some of the best choices for treatment of severe gram-negative infections.[1–3] Despite the large number of antibacterial agents that have appeared over the last few years as alternatives to aminoglycosides, the latter still play an important role in clinical practice. The aminoglycosides, in comparison with other antimicrobial agents that rapidly select for resistant mutants (e.g., β-lactams and fluoroquinolones), are predictably effective for many aerobic gram-negative pathogens.[4–6]

One of the primary reasons for limiting clinical use of the aminoglycosides is the nephrotoxicity observed with conventional multiple daily dosing.[1,6] Over the past several years, much has been learned about the efficacy and toxicities of the aminoglycosides, and a new dosing strategy has emerged using single daily dosing (SDD).[3,5,6] Practitioners are encouraged to reevaluate the utility of the aminoglycosides as an important component of the modern antimicrobial arsenal.

196.3 MECHANISM OF ACTION

The aminoglycosides are bactericidal agents.[1,6] They penetrate the bacterial cell wall and membrane, and impair protein synthesis by binding to components of the prokaryotic 30s ribosomal subunit.[5,6] This binding leads to bacterial misreading of messenger ribonucleic acid (mRNA), with subsequent production of nonfunctional proteins, detachment of ribosomes from mRNA, and cell death.[5]

196.4 SPECTRUM OF ACTIVITY

Aminoglycosides are effective against most community-acquired gram-negative aerobes and select gram-positive pathogens. Organisms commonly susceptible to these drugs include *Klebsiella, Citrobacter, Enterobacter, Serratia,* and most *Acinetobacter* spp.[1,5] They are frequently, although not uniformly, effective against *Pseudomonas aeruginosa* and *Escherichia coli*. [1,3]

Aminoglycosides are not active against anaerobes because their uptake across bacterial cell membranes depends on energy derived from aerobic metabolism.[3] This dependence on aerobic metabolism is the cause of markedly reduced activity of these agents in areas of low pH and oxygen tension, such as abscesses and other infected hypoxic tissues.[1,3]

Among gram-positive organisms, the aminoglycosides, particularly gentamicin, are active against many *Staphylococcus* spp. Other gram-positive organisms, such as *Streptococcus* spp and many enterococci, are relatively resistant.

Studies of bacteria in cell culture have shown that combining an aminoglycoside with a β-lactam agent results in bacterial killing superior to the simple added activity of each of these antimicrobials, a phenomenon termed *synergism*. [1,3] The efficacy of the aminoglycosides appears to be enhanced by increased cell permeability induced by the β-lactam antibiotic, favoring the uptake of the aminoglycoside into certain bacteria. Classically, synergy is observed between penicillins and gentamicin toward susceptible strains of *Enterococcus faecium* and *Enterococcus faecalis,* although synergy has also been described for gram-negative pathogens, including *Pseudomonas aeruginosa*. [1,7] Synergism is particularly important in cases of partial resistance to gentamicin, and when low tissue pH and low oxygen tension (e.g., abscesses or tissue hypoxia) decrease aminoglycoside transport into bacteria.

The aminoglycosides are active against some mycobacteria, as well as less common pathogens such as *Yersinia pestis, Brucella* spp, and *Francisella tularensis*. [1,3] Amikacin and gentamicin are used in similar circumstances, often interchangeably.[3] Amikacin, however, is not degraded by the common enzymes that degrade gentamicin and therefore has a broader spectrum of activity.[3] It is the preferred agent for serious nosocomial infections caused by *Klebsiella* spp and *Pseudomonas aeruginosa*. [1,3]

196.5 INDICATIONS

The aminoglycosides are used for short-term (≤7 days) treatment of infections caused by susceptible strains of gram-negative microorganisms that are resistant to less toxic antibiotics.[8,9] They are useful for severe infections of 830 the abdomen, urinary tract, pulmonary parenchyma, endocardial valves, bloodstream, and surgical wounds.[3,10] The 831 introduction of extended-spectrum β-lactam antibiotics and fluoroquinolones, all of which have a greater safety profile than the aminoglycosides, has necessitated a critical reappraisal of the indications for aminoglycoside therapy.[4,7]

Monotherapy with an aminoglycoside is seldom appropriate in critically ill patients.[7] Aminoglycosides traditionally have been administered in combination with another antimicrobial agent to enhance bactericidal activity and minimize resistance.[1,5,10] More specifically, in patients with life-threatening infections in which mixed organisms are suspected, aminoglycosides are appropriately administered with a β-lactam, β-lactam/β-lactamase inhibitor or a carbapenem.[3,5,10] This approach provides not only synergistic bacterial activity but also antibacterial coverage during the aminoglycoside-free interval when using SDD.[1] Although this remains a time-honored and rational strategy, the authors of a recent large-scale metaanalysis of antibiotic usage concluded that the addition of an aminoglycoside to a broad-spectrum β-lactam conferred no benefit to any subset of septic patients when compared with β-lactam monotherapy.

Metronidazole or clindamycin may be prescribed in combination with an aminoglycoside when coinfection with strict anaerobic pathogens is suspected. For partially susceptible *Enterococcus* spp, gentamicin must be coadministered with a β-lactam agent to facilitate penetration of the aminoglycoside into the cell.[1,3] The initial antibiotic regimen in a given patient should always be modified on the basis of response to therapy and microbiologic data. Patients receiving parenteral aminoglycosides should be well hydrated and should have stable renal function and an inactive urine sediment.[1,2,6]

Aerosolized gentamicin may be administered to patients with susceptible pulmonary infections with limited risk of systemic absorption and toxicity.[1,5,11] The efficacy of inhalational therapy with aminoglycosides has not been studied critically in dogs and cats, although aerosolized gentamicin appears to decrease the clinical signs associated with *Bordetella bronchiseptica* infection in dogs.[11]

Aminoglycosides are poorly absorbed following oral administration but may act within the gastrointestinal tract, largely preventing systemic toxicity. Oral neomycin is prescribed to suppress bacterial growth in the large bowel, and paromomycin is effective for enteric salmonellosis and protozoal enteritis in companion animals.[1,12] Although serum levels of neomycin and paromomycin generally are negligible in healthy animals, significant systemic absorption and toxicity are possible when the intestinal epithelial barrier is diseased or compromised.[1,9,12]

196.6 PHARMACOLOGY AND DOSING

The aminoglycosides are highly water soluble and do not readily cross biologic membranes.[1] As such, they are largely confined to the extracellular fluid and have correspondingly small volumes of distribution (Vd).[4] The aminoglycosides are mainly eliminated unchanged in the urine. They are excreted predominately by glomerular filtration, with a small fraction (<5%) undergoing tubular reabsorption.[2,3,6] Penetration into cerebrospinal fluid, prostate, and vitreous humor is minimal, and their efficacy is not reliable in these tissues.[1,3] Therapeutic concentrations are generally achieved in nonexudative pleural and peritoneal effusions, bones, and synovial fluid.[1] Following parenteral administration, adequate tissue levels are generally achieved in the pulmonary parenchyma but not in bronchial secretions. They are usually are ineffective for intracellular pathogens.

The rate and extent to which an aminoglycoside achieves bacterial killing is a function of its concentration.[4,6,10,13,14] For many years, the aminoglycosides were administered in multiple daily doses.[3,13] However, many in vitro and in vivo studies suggest that administration as an SDD is equally or more effective than conventional regimens and reduces the associated toxicities.[3,10,13] SDD implies that the total daily dosage is administered as a single dose approximately every 24 hours, rather than in multiple divided doses. With concentration-dependent antibacterial activity, the rate and extent of bacterial cell death increases with the higher drug concentrations achieved with SDD, in addition to producing more favorable outcomes and fewer resistant organisms.[1,4,10,13]

Aminoglycosides provide a PAE, which means that bacterial replication is impeded even after serum drug concentrations have fallen below the minimum inhibitory concentration (MIC) of the organism in question (Figure

196-1).[1,3,4,6] This permits longer dosing intervals. The postantibiotic effect (PAE) tends to be longer in vivo than in vitro.[1] Aminoglycosides possess a PAE that is linked to (1) the species of bacteria, (2) the MIC of the bacterial strain, and (3) the concentration of drug achieved at the site of infection.[6] The PAE demonstrated by aminoglycosides is one component of SDD that allows extended drug-free intervals without compromising patient outcome, and it may be enhanced by higher dosages and concurrent administration of a cell wall–active antibiotic such as a β-lactam.[13]

Aminoglycosides are associated with a first-exposure effect called *adaptive resistance,* which is most relevant for gram-negative organisms, including *P. aeruginosa.* [3] This phenomenon is manifested after the first dose by down-regulation of aminoglycoside uptake for subsequent doses (see Figure 196-1). When this occurs, there is less bacterial killing with the later doses, as well as shorter PAEs. It is most likely to occur with first doses that provide low peak serum concentrations (C_{max}). Once the first exposure develops, the downregulation can last for hours. SDD provides the high serum concentrations necessary to prevent inducing a first-exposure effect, extends the interval between doses to overcome the onset of adaptive resistance, and decreases the incidence of nephrotoxicity.[5]

The therapeutic efficacy of the aminoglycosides is correlated with the C_{max}, and the adverse effects are corrected to trough concentrations.[4,14] Concentration-dependent bactericidal activity is optimized by attaining a C_{max} that exceeds the MIC by a factor of 8 to 10.[10,14] The C_{max}-to-MIC ratio is sometimes referred to as the *inhibitory quotient*. The goal of SDD is to obtain a high C_{max} while maintaining a drug-free interval of at least 2 to 4 hours (see Figure 196-1). Because of interpatient variability in Vd and renal function, TDM has been the standard of care in patients receiving traditional multiple daily dosing regimens to ensure adequacy of peak concentrations and prevent toxicity.[1,5,10,14] Rapid turnaround time is crucial if changes are to be made in the regimen before the next scheduled dose.[8] Very few veterinary centers have the benefit of same-day results, effectively precluding the utility of TDM in critically ill companion animals. TDM is not uniformly recommended with SDD unless therapy beyond 5 to 7 days is anticipated or for patients at greater risk of toxicity, such as those receiving other nephrotoxic drugs 831 832 or those with known or suspected preexisting renal impairment.[14] When feasible, TDM recommendations for SDD include obtaining a peak sample 20 to 30 minutes after the intravenous infusion of the drug, and at least two additional samples during the elimination phase of the drug, at 2 and 4 hours after infusion. From this information, the drug's Vd, clearance, and half-life may be calculated to determine the most appropriate dosing regimen for a given patient.[10]

Figure 196-1 Graphic hypothetical representation of serum drug concentration versus time following bolus intravenous administration of an aminoglycoside illustrating peak serum concentrations *(C_{max})*, minimum inhibitory concentration *(MIC)*, postantibiotic effect, and adaptive resistance. See section in this chapter entitled Pharmacology and Dosing for details.

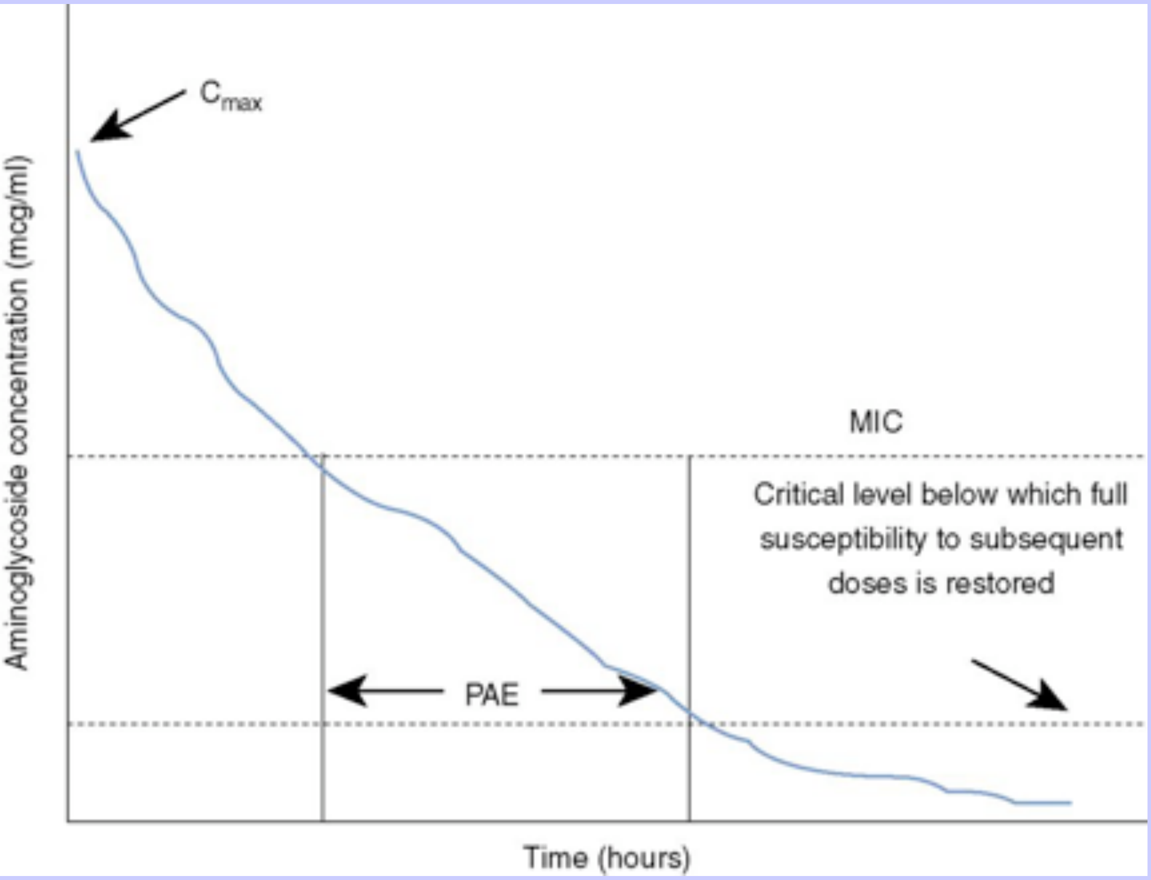

Table 196-1 Aminoglycoside Monitoring Guidelines

Drug	Dosage	Interval	Peak Concentration*	Trough Concentration†
Amikacin	15 mg/kg	q24h	30 to 40 μg/ml‡	≤2.5 μg/ml or undetectable
Gentamicin	6.6 mg/kg	q24h	15 to 20 μg/ml‡	≤1 μg/ml or undetectable

This is often impractical, and values can vary significantly on a day-to-day basis in critically ill patients.[4,10] An acceptable simplified strategy is to obtain a peak sample 20 to 30 minutes after intravenous administration and a trough serum sample 2 to 4 hours before the next dose, to ensure adequate renal clearance that provides a sufficient drug-free period.[10] Trough serum drug concentrations correlate with nephrotoxicity and should be below the limit of detection for most commercial assays. A trough of 1 µg/ml or greater with gentamicin or 2.5 µg/ml or greater with amikacin is indicative (and not a cause) of renal dysfunction, and this should prompt the clinician to discontinue the aminoglycoside and pursue another drug class.[4,6]

A high inhibitory quotient must be achieved with aminoglycoside therapy to reliably kill the offending organism.[4,10] Pharmacokinetic studies using SDD of gentamicin have been completed in healthy dogs, revealing sufficient peak serum levels for the treatment of most pathogens.[14] However, the initial dose of gentamicin or amikacin necessary to provide adequate peak concentrations in critically ill dogs and cats using SDD has not been evaluated. Moreover, obtaining a C_{max} is useful only if the result is compared with the MIC of the pathogen in question. For example, if an organism has an MIC of 2 µg/ml, a C_{max} of 20 µg/ml is expected to provide an appropriate inhibitory quotient of 10. This is almost invariably achieved using SDD, but exceptions occur, particularly in critically ill patients in which a drug's Vd is unpredictable.[4,10]

Extensive fluid extravasation, edematous states, and hypoalbuminemia often are associated with critical illness and an increase in Vd.[4,10] Other causes for alterations in Vd include hyperdynamic states occurring in patients with a systemic inflammatory response syndrome (e.g., sepsis, pancreatitis), mechanical ventilation, extensive burn injuries, and severe trauma.[4] Aggressive intravenous fluid therapy and parenteral nutrition further contribute to expanding extracellular water and essentially dilute aminoglycosides in the extracellular compartment of many critically ill patients.[4] More specifically, an enlarged Vd associated with any of the above conditions may result in subtherapeutic aminoglycoside serum levels in septic patients.[4,10]

TDM should be used to guide proper drug dosing in such cases (Table 196-1).[4,10] A random sample obtained 8 to 832
12 hours following administration may be helpful to prevent a prolonged drug-free period. Anticipated trough 833
levels should not be reached by this time in patients with normal renal function.[3,4] However, if serum levels exceed 8 µg/ml for amikacin or 3 µg/ml for gentamicin, impaired renal clearance should be suspected, prompting modification of the dosing regimen or discontinuation of the aminoglycoside.[3] For all patients receiving aminoglycosides, most human hospitals employ specific nomograms based on an individual's serum drug level(s), creatinine clearance, lean body weight, body surface area, gender, and other variables.[4,10] Similar formulas have not been implemented for companion animals, and moreover the nomograms are not suitable for septic patients.[4,10]

Although SDD may obviate the need for TDM in many human patients, this has yet to be confirmed by clinical studies in dogs and cats.[5,6,13] Veterinarians are encouraged to incorporate TDM into their practice, if even on an intermittent basis, because goal-oriented dosing of aminoglycosides is expected to result in enhanced antibiotic efficacy and reduced incidence of toxicity in critically ill patients.[8,10]

Gentamicin and amikacin are the most frequently used parenteral aminoglycosides in veterinary medicine. Netilmicin, streptomycin and tobramycin have been evaluated in companion animals but are seldom used. Gentamicin and amikacin commonly are administered intravenously over 20 minutes, although bolus administration is described and well tolerated.[4] The recommended starting dosage for gentamicin is 6.6 mg/kg IV q24h. Amikacin is administered initially at 15 mg/kg IV q24h. The dosage for obese animals should be based on lean body weight.[1]

The intravenous route is the preferred method of aminoglycoside drug administration in critically ill patients. Patients should be simultaneously receiving sodium-replete intravenous fluids, particularly if there is any question regarding hydration or intravascular volume status. Amikacin and gentamicin are well absorbed following intramuscular and subcutaneous administration in well-hydrated and well-perfused animals.[1] However, these routes of administration are associated with discomfort at the injection site, and absorption is less predictable when compared with the intravenous route.[14]

Aerosolized antibiotic therapy remains largely unproven for lower respiratory tract infections in animals. This mode of delivery is particularly intriguing for the aminoglycosides because of their limited penetration into respiratory secretions when administered systemically. Limited data support the use of aerosolized gentamicin for inhalation as adjunctive therapy in canine patients infected by *B. bronchiseptica*. [1,11] Injectable gentamicin (6 to 7 mg/kg) combined 1:3 sterile saline is administered with an upstream nebulizer for approximately 10 minutes, 2 to 3 times daily. Systemic absorption is generally negligible.[1] Use of aerosolized aminoglycosides may be reserved for select patients with pulmonary infections that are highly resistant or unresponsive to aggressive conventional therapies, recognizing that it is not known how well or to what extent nebulized agents are distributed to affected pulmonary tissues. Additionally, topical delivery is never adequate alone and systemic antimicrobials must be administered simultaneously. It remains to be seen if there is a place for nebulization of aminoglycosides to dogs and cats with mild to moderately severe lower respiratory tract infections, or to intubated patients with severe or ventilator-associated pneumonia.

* Extrapolated from Clinical and Laboratory Standards Institute guidelines, assuming a breakpoint minimum inhibitory concentration of ≤8 μg/ml for amikacin and ≤2 μg/ml for gentamicin.

† Obtain sample 30 minutes after intravenous injection or 60 minutes after intramuscular injection.

† Obtain sample 2 to 4 hours before next dose is to be administered.

196.7 ADVERSE EFFECTS

Toxic side effects of the aminoglycosides generally involve the neuromuscular junction, inner ear apparatus, and, most significantly, the renal proximal convoluted tubules.[3,9]

Reversible neuromuscular paralysis is uncommon and thought to result from interference with release of acetylcholine and uptake of acetylcholine at the neuromuscular junction.[6,9] The aminoglycosides may also inhibit calcium movement into the nerve terminal on depolarization; calcium is required for subsequent release of acetylcholine. Weakness may be produced at dosages just slightly higher than those recommended, but is likely to be of clinical consequence only in patients with neuromuscular disorders such as myasthenia gravis or that are receiving neuromuscular blocking agents.[1,5,15] Injectable calcium reverses the neuromuscular paralysis produced by aminoglycosides.[5] A cholinesterase inhibitor such as neostigmine also has an antidotal effect.[9]

Aminoglycosides can cause both cochlear and vestibular toxicities by accumulating in the affected tissue and destroying the sensory hair cells.[9] Numerous animal studies using prolonged or very high doses, or both, of aminoglycosides administered by a variety of routes reveal that both dogs and cats are susceptible to irreversible aminoglycoside-induced ototoxicity.[9] There appear to be no standards established for assessing, measuring, or defining aminoglycoside-related ototoxicity in companion animals. Moreover, there are scant reports in the literature of drug-induced vestibulocochlear damage in dogs or cats receiving recommended therapeutic dosages of amikacin or gentamicin.[9,12] In the human literature, the incidence of ototoxicity has not been shown to be significantly different with SDD. Rather, the risk of ototoxicity seems to be related to the duration of treatment with aminoglycosides.

Nephrotoxicity as evidenced by nonoliguric renal insufficiency is a well-known consequence of aminoglycoside administration.[1,6,8,15] Aminoglycosides damage the cells of the proximal renal tubules and reach maximal tubular toxicity around day 9 of therapy.[1,2] The cationic state of the aminoglycosides facilitates binding to tubular epithelial cells.[6] Intracellular transport results in high concentrations of the aminoglycoside within lysosomes. Lysosomes eventually destabilize and rupture, disrupting normal cell structure and function.[2,6,8] The resulting decline in glomerular filtration is likely multifactorial in origin and involves both tubular and nontubular mechanisms.[8]

Results from animal studies suggest that gentamicin is more nephrotoxic than amikacin.[1,6] However, it is not clear if any real difference exists between the toxicities of the two drugs in the clinical setting, and both have the potential to cause tubular damage.[5,6] The physiologic manifestations of nephrotoxicity are varied and often clinically undetectable until extensive injury has occurred.[2,6] Clinically, nephrotoxicity generally manifests as polyuric renal failure, with varying degrees of renal dysfunction.[2,8] Glomerular filtration rate decreases as a relatively late event, usually at least 5 to 7 days after initiating therapy. SDD is associated with a lower incidence of nephrotoxicity than when the same amount of medication is given in multiple doses.[1-3,10,13] Why this regimen is less nephrotoxic is not completely understood, but it is believed to be due to less uptake of the drug by renal cortical tissue. Less-frequent administration limits drug accumulation in the renal cortex because the uptake of the aminoglycosides appears to be a saturable process.

An area of interest related to aminoglycoside toxicity is the correlation with circadian variation in glomerular filtration.[16,17] Temporal variations in renal toxicity of the aminoglycosides are reported for animals and humans. In diurnal mammals, glomerular filtration rate is slower at rest (at night).[3] An increased incidence of renal toxicity is observed when the drug is injected during the rest period, and lower toxicity is observed when the aminoglycoside is administered during periods of activity (i.e., during the day).[3,16,17] Moreover, administering gentamicin during the day appears to be more effective.[16] Further investigations are necessary to understand and confirm this phenomenon in dogs and cats with naturally occurring illness.

Evaluating for elevations in blood urea nitrogen and creatinine are not appropriate to screen for early renal damage.[1–3,6] By the time azotemia is evident, significant intrinsic renal injury already exists and, by definition, the patient is in renal failure.[8] Critically ill patients are invariably receiving intravenous fluids, and thus evaluation of urine concentrating ability is of limited utility in assessing for drug-induced renal damage. Enzymuria, the appearance of brush border–derived enzymes such as N-acetyl-β-D-glucosaminidase and γ-glutamyl-transpeptidase, is one of the earliest signs of aminoglycoside-induced renal damage, but routine measurements are impractical.[1,2,6]

Examination of the urine sediment for granular or cellular casts on a daily basis is recommended.[1,8,14] Ideally, the sediment is examined within 1 or 2 hours of obtaining a urine sample because casts very often dissolve. Urine reagent strips should also be evaluated, because glucosuria and tubular proteinuria may be seen with aminoglycoside-induced renal injury.[6,14] Although some reports describe an inexorable progression of aminoglycoside-induced renal injury and an associated poor prognosis, it is felt that tubular lesions are often reversible and renal function recovers if tubular injury is detected early and therapy discontinued promptly.

Advanced age, duration of therapy, fever, volume depletion, and dehydration increase the risk of aminoglycoside-induced nephrotoxicity.[2,8] Other risk factors include concomitant administration of nephroactive drugs (e.g., cisplatin, nonsteroidal antiinflammatory drugs, diuretics (e.g., furosemide), angiotensin-converting enzyme inhibitors), preexisting renal disease, and potassium and magnesium depletion.

Penicillins should not be mixed in the same syringe with an aminoglycoside because this inactivates the aminoglycoside. Aminoglycosides should not be administered intravenously with solutions containing calcium, sodium bicarbonate, or heparin.[1] The aminoglycosides should be given only when their unique antibiotic potency is needed, such as treatment of nosocomial infections that are not susceptible to less toxic antibiotics.[2,7,10]

196.8

SUGGESTED FURTHER READING*

JL Gookin, JE Riviere, BC Gilger, MG Papich: Acute renal failure in four cats treated with paromomycin. *J Am Vet Med Assoc*. **215**, 1999, 1821, 1806, 1999 *Case series that underscores the risk of systemic toxicity when aminoglycosides are administered orally to patients with a compromised gastrointestinal mucosal barrier*.

CE Greene, DJ Watson: Antibacterial chemotherapy. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. ed 3, 2006, Saunders, St. Louis, *A chapter on antimicrobials in this authoritative text that provides a clear updated review of the aminoglycosides*.

SI Rubin, MG Papich: Acute renal failure in dogs: a case of gentamicin nephrotoxicity. *Comp Cont Educ Sm Anim Pract*. **9**, 1987, 510, *A case report that includes an outstanding discussion of the pathophysiology and expected timeframe for the development of drug-induced renal lesions in companion animals*.

* See the CD-ROM for a complete list of references

197 Chapter 197 Fluoroquinolones

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197.1 KEY POINTS

- Fluoroquinolone antibiotics exhibit bactericidal properties through their inhibition of deoxyribonucleic acid gyrase and topoisomerase IV.
- Fluoroquinolones are extremely bioavailable and exhibit a high degree of efficacy at relatively low tissue concentrations.
- They are useful for gram-negative and staphylococcal bacterial infections. They have variable efficacy against *Streptococcus* spp. and intracellular pathogens.
- Fluoroquinolones have excellent tissue penetration, particularly in the urinary tract, prostate, lung, bile, and inflammatory cells.
- Bacteria are developing resistance to fluoroquinolones.
- Adverse effects of fluoroquinolone antimicrobials include primarily vomiting, diarrhea, nausea, abdominal pain, and cartilage defects. Blindness has occurred in cats.

197.2 INTRODUCTION

The fluoroquinolone antimicrobial drugs were introduced into clinical medicine approximately 20 years ago. These agents were regarded initially as model antimicrobial agents because of their broad spectrum of activity, favorable pharmacokinetics, and low incidence of toxicity. The fluoroquinolone antimicrobials are entirely synthetic; all possess a common structure containing a 4-quinolone nucleus. Although the more rarely used first-generation fluoroquinolones (nalidixic acid, flumequine) possess a limited spectrum of activity, structural modification of the quinolone nucleus has resulted in an increase in potency and a diversification of spectrum in subsequent generations.

As a class, they are well absorbed after oral and parenteral administration, have a large volume of distribution, and have extended elimination half-lives, allowing for longer dosing intervals. Fluoroquinolones are bactericidal antibiotics at relatively low tissue concentrations and have a favorable margin of safety. Adverse effects in veterinary medicine are associated most frequently with the gastrointestinal (GI) system; however, these agents have been associated with orthopedic, ophthalmologic, neurologic, renal, and cardiac toxicity. This chapter reviews chemical, microbiologic, pharmacokinetic, pharmacodynamic, clinical aspects, and toxicity associated with fluoroquinolone use.

197.3 STRUCTURE AND PHYSICAL PROPERTIES

Fluoroquinolones are weak organic acids. They have amphoteric properties as a result of having an acidic group (carboxylic acid) and a basic group (tertiary amine); they are soluble in both alkaline and acidic solutions. All quinolone derivatives in clinical use have a dual ring structure with a nitrogen at position 1, a carbonyl group at position 4, and a carboxyl group attached to the carbon at the 3 position of the first ring (Figure 197-1).[1]

Earlier fluoroquinolones, such as nalidixic acid, did not achieve systemic antibacterial levels. As a result, these agents had limited clinical utility and were suitable only for treating lower urinary tract disease. Fortunately, several structural modifications to the original dual ring have resulted in increased potency, extended spectrum, and enhanced bioavailability. For example, the addition of a fluorine at position 6 led to increased efficacy against both gram-negative and gram-positive bacteria, and substitutions at position 7 result in increased potency and increased antipseudomonal activity. At position 8, addition of a halide, fluorine, or a methoxy group enhances activity against anaerobic bacteria (see Figure 197-1).[1] A more extensive discussion of the relationships between structure and activity of the quinolone class is beyond the scope of this chapter.

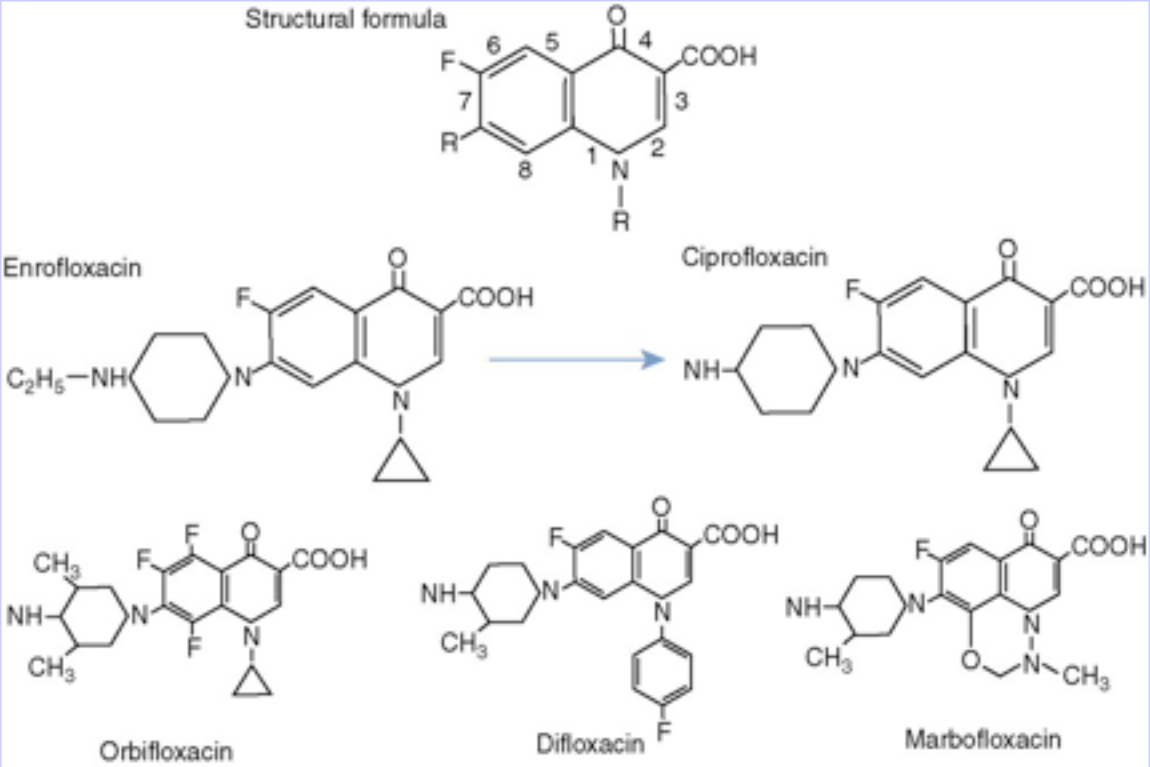
Five fluoroquinolones are marketed for use in small animals: ciprofloxacin, marbofloxacin, ibafloxacin, enrofloxacin, and difloxacin. All of these agents are considered third-generation fluoroquinolones. Within this class, important differences exist in the rate and extent of biotransformation, rate of elimination, and method of excretion. For example, approximately 40% of enrofloxacin is metabolized to ciprofloxacin; difloxacin is metabolized extensively and excreted as a glucuronide conjugate in bile, with no detectable urine concentrations; and approximately 40% of marbofloxacin is excreted unchanged by the kidney.[2–4]

197.4 MECHANISM OF ACTION

Fluoroquinolone antibiotics exert their antimicrobial effect by inhibiting two enzymes of the topoisomerase class: DNA gyrase, or bacterial topoisomerase II, and topoisomerase IV. It is thought that DNA gyrase is the primary quinolone target for gram-negative bacteria, and topoisomerase IV is the target for gram-positive bacteria. For bacterial replication to proceed, individual strands of bacterial DNA must be separated. This results in “supercoiling,” or excessive positive coiling, of DNA strands in front of the replication fork. DNA gyrase is responsible for inducing continuous negative supercoils in the bacterial DNA strand. In addition, DNA gyrase is responsible for removing positive superhelical twists that accumulate ahead of the DNA replication fork through the breakage of both strands of duplex DNA, passage of another segment of DNA through the break, and resealing of the break.[1] Both of these actions help to relieve the topologic stress of replication.

DNA gyrase is composed of two subunits (A and B) that must function together for supercoiling to proceed. The A subunit, which is responsible for the strand-cutting function of the gyrase, is the presumed site of action of the quinolones.[1] Although inhibition of DNA gyrase leads to functional disturbances that result in rapid death of bacteria, the molecular mechanisms responsible for this bactericidal effect are still not incompletely understood.

Figure 197-1 All quinolone derivatives in clinical use have a dual ring structure with a nitrogen at position 1, a carbonyl group at position 4, and a carboxyl group attachedto the carbon at the 3 position of the first ring. The structural modifications to the original dual ring tocreate many of the available quinolone antibiotics are shown in thisfigure.



Quinolones also inhibit the activity of topoisomerase IV. Topoisomerase IV resolves (decatenate) interlinked (catenated) daughter DNA molecules to facilitate their segregation into their respective daughter cells following replication.[1] Inhibition of topoisomerase IV is responsible for the bactericidal effect of the quinolones on gram-positive bacteria.

197.5 SPECTRUM

Although the fluoroquinolone antibiotics all possess the same basic chemical structure, agents within the class exhibit variability in their spectrum and potency (Table 197-1). These antibiotics differ from other antibiotics such as penicillins, tetracyclines, and macrolides in that they exhibit a high degree of efficacy at relatively low serum concentrations. In addition, minimal bactericidal concentrations of quinolones are usually within two-fold to four-fold of the minimum inhibitory concentration (MIC) for many of their target organisms.

As a class, the fluoroquinolones are highly effective against aerobic gram-negative bacteria, including the Enterobacteriaceae, *Mannheimia (Pasteurella) haemolytica, Pasteurella multocida, Haemophilus somnus, Bordetella,* and *Campylobacter,* among others.[7] Different fluoroquinolones exhibit variable activity against *Pseudomonas* spp, with ciprofloxacin and levofloxacin as the only quinolones with sufficient potency for use against susceptible strains of *Pseudomonas aeruginosa* in human medicine. Some of the newer quinolones are active against gram-positive bacteria, including *Staphylococcus aureus, Staphylococcus epidermidis,* and *Neisseria.*[7] Activity against the *Streptococcus* spp is limited to a small subset of quinolones, although some newer agents are addressing this deficiency. In general, fluoroquinolones available for veterinary use have limited anaerobic activity. Because of their ability to penetrate phagocytic cells, fluoroquinolones have activity against many intracellular pathogens, including *Mycoplasma, Chlamydia,* and *Brucella.*[7]

197.6 PHARMACOKINETICS

Fluoroquinolones are highly bioavailable after both oral and parenteral administration and exhibit excellent tissue distribution. They are absorbed rapidly after oral administration, with peak serum levels attainable within 0.5 to 2 hours.[5] Quinolone bioavailability may vary between 35% and 100%, depending on the species. Table 197-2 summarizes dosing recommendations and peak serum concentrations of commercially available fluoroquinolones labeled for use in small animal patients. Administration of oral antacids containing polyvalent cations (magnesium, aluminum, calcium, iron, and zinc) decreases absorption of quinolone antimicrobial drugs. Food intake does not tend to decrease total serum concentrations of fluoroquinolones, provided the ingested food does not contain large amounts of magnesium or aluminum ions, but it may delay peak serum concentrations.[1]

Following administration, the quinolones tend to exhibit rapid and extensive tissue distribution. Concentration of quinolone antimicrobials in urine, kidney, lung, prostatic tissue, stool, bile, macrophages, and neutrophils often exceeds that in serum.[5] For example, quinolone concentrations achieved in bile and urine are often 10 to 20 times greater than those in serum. Because these agents are concentrated in phagocytic cells, they reach higher concentrations at inflammatory sites.[6] Concentrations of quinolones in saliva, prostatic fluid, bone, and cerebrospinal fluid are usually lower than drug concentrations in serum, although they are often adequate for susceptible organisms, particularly in the presence of inflammation.[1] Fluoroquinolones are partially metabolized by the liver, and they are excreted in bile or urine unchanged or as metabolites. Depending on the primary mode of excretion, dosage reductions should be considered in animals with renal or hepatic disease.[5] 836

Table 197-1 Relative Activity of Veterinary Quinolones Against Bacteria Isolated From Animals, as Determined by MIC 90*

	Concentrations (µg/ml)			
Organism	**Difloxacin**	**Enrofloxacin**	**Marbofloxacin**	**Orbifloxacin**
Gram Negative				
Escherichia coli	0.25 to 16	0.06 to 20	0.06 to 20	0.5 to 4
Klebsiella pneumoniae	0.5	0.12 to 0.25	0.01 to 0.06	0.25
Proteus spp	1	0.25 to 0.5	0.125	1
Pasteurella multocida	—	0.016 to 0.03	<0.008 to 0.5	ND
Salmonella spp	0.125	0.03 to 0.25	0.03	0.25
Bordetella bronchiseptica	4	0.5	0.5	2
Pseudomonas aeruginosa	4 to 8	1 to 8	0.06 to 4	4 to 16
Gram Positive				
Staphylococcus intermedius	1	0.12 to 0.5	0.25	0.5
Staphylococcus aureus	1	0.12	0.25 to 0.5	0.5
Enterococcus spp	ND	1 to 2	1 to 4	16 to 32
β-Hemolytic *Streptococcus*	ND	ND	2	1 to 2
Anaerobes				
Clostridium	ND	0.5	ND	ND
Bacteroides	ND	0.5	ND	ND
Porphyromonas gingivalis	ND	1.5	ND	ND
Bifidobacterium	ND	2	ND	ND
Prevotella oralis	ND	1	ND	ND

From Greene CE, Watson ADJ, Greene CE, editors: *Infectious diseases of the dog and cat,* ed 3, St Louis, 2006, Saunders.

MIC, Minimum inhibitory concentration; *ND,* no data available.

Fluoroquinolone antibiotics exhibit concentration-dependent bacterial killing. Therefore high peak tissue concentrations and persistence of antibiotic concentration above the MIC value for a given organism determine their in vivo efficacy. The total amount of drug given daily, rather than the dosing schedule, determines their in vivo potency.

The fluoroquinolones marketed for veterinary use have relatively long half-lives; they often are administered once or twice daily to achieve appropriate serum concentrations. The antibacterial action of the fluoroquinolones is considered biphasic. During the first phase, the percentage of bacteria killed increases with increasing concentration of antibiotic. During the second phase, further increases in the concentration cause a temporary decrease in the percentage of bacteria killed.[1] In addition, fluoroquinolones exhibit a marked postantibiotic effect in which they continue to inhibit bacterial growth up to 8 hours after being eliminated from the body.[6]

The quinolone antibiotics exhibit synergy with several other classes of antibiotics; however, their synergistic effects vary in different bacterial infections. Typically they are synergistic with antipseudomonal penicillins, ceftazidime, imipenem, and occasionally rifampin and the aminoglycosides.

* Lower concentration indicates greater susceptibility.This table should be used as a guide to efficacy. Isolates of the same bacterial species can differ intheir antimicrobial resistance depending on differences in time, geography, laboratory methodology, and prior exposure to antimicrobial drugs.

197.7 RESISTANCE

Because fluoroquinolone antimicrobials are being used more routinely, resistant organisms are emerging at an increased frequency, particularly among *Staphylococcus, Pseudomonas,* and *Serratia*. Resistance to fluoroquinolones is due exclusively to chromosomal alterations. These alterations may result in changes in the target enzymes, specifically DNA gyrase and topoisomerase IV, changes in the permeability of the microbial cell wall to fluoroquinolones, or an increase in the expression of efflux systems resulting in a reduction of intracellular concentration of antibiotic.[8]

Resistance to one fluoroquinolone usually confers cross-resistance to all other members of the class. A retrospective study evaluating resistance among canine urinary tract isolates from 1992 to 2001 showed a significant increase in resistance in species of *Proteus, Staphylococcus intermedius,* and *Escherichia coli* for either enrofloxacin or ciprofloxacin.[9] However, a more recent study evaluating the in vivo efficacy of marbofloxacin against bacterial isolates from urinary, respiratory, and skin samples did not identify a significant increase in resistance over a 7-year period.[10] To minimize the development of resistance, fluoroquinolone antibiotics should not be used as first-line agents for infections that will likely be susceptible to other antibiotics. In addition, adherence to pharmacokinetic and pharmacodynamic parameters of specific antibiotics is important in preventing the selection and spread of resistant strains of bacteria.

197.8 CLINICAL USES

Because fluoroquinolone antimicrobial agents penetrate nearly every tissue in the body, they can be used to treat a 837 wide variety of infections. They are highly bioavailable and have favorable pharmacokinetic properties that allow 838 for once-daily dosing in many patients. In veterinary medicine, they are used most frequently to treat infections of the urinary tract, respiratory tract, skin, GI tract, and bone. At therapeutic dosages, quinolones are relatively safe, and there are few reported adverse effects.

Table 197-2 Peak Serum Concentrations of Quinolones in Dogs and Cats

Drug	Species	Route	Dosage (mg/kg)	Peak Serum Concentration (μg/ml)
Difloxacin	Dogs	PO	5	1.1 to 1.8
			10	3.6
Enrofloxacin	Dogs	PO	2.75	0.7
			5	1.2 to 1.41
			5.5	1.4
			7.5	1.9
		SC	20	4.4 to 5.2
			5	1.3
		IV*	5	1.827
			20	161
Marbofloxacin	Dogs	PO	1	0.8
			2	1.4 to 1.47
			2.5	2
			2.75	2
			4	2.9
			5	4.2
			5.5	4.2
Orbifloxacin	Dogs (cats)*	PO	2.5	1.37 to 2.3 (1.6 to 2.1)*
			7.5	6 to 6.9 (5)*
Ibafloxacin	Dogs	PO	7.5	3.72
			15	6.04
			30	12.15
Ciprofloxacin*	Dogs	IV	10	7.8

From Greene CE, Watson ADJ, Greene CE, editors: *Infectious diseases of the dog and cat,* ed 3, St Louis, 2006, Saunders.

IV, Intravenous; *MIC*, minimum inhibitory concentration; *PO*, per os.

The bacteria most commonly associated with infections of the urinary tract in the dog include *E. coli, Staphylococcus, Streptococcus, Klebsiella, Proteus,* and *Pseudomonas*. All of these bacteria have been treated successfully with fluoroquinolone antibiotics. Because fluoroquinolones are concentrated in the urine, several agents within this class are effective for bacterial cystitis in both the dog and the cat.[9] Enrofloxacin reaches concentrations in prostatic tissue greater than those in serum and is therefore very effective for treating bacterial prostatitis in the dog.[11]

Fluoroquinolone antibiotics accumulate in lung tissue to levels greater than that found in serum in most domestic animal species. Several fluoroquinolone antibiotics are effective against respiratory pathogens such as *Pasteurella, E. coli,* and *Bordetella* in the dog and cat. In humans, the primary limitation to using fluoroquinolone antibiotics for community-acquired pneumonia is the limited in vitro susceptibility of ciprofloxacin, ofloxacin, and norfloxacin against *S. pneumoniae* and anaerobic bacteria. However, some of the newer fluoroquinolones, such as gatifloxacin and levofloxacin, have enhanced gram-positive and anaerobic spectra, and thus may be more effective for treating pneumonia in humans.[12] Further studies are needed to delineate whether these fluoroquinolones are safe and effective for use in veterinary patients.

Fluoroquinolone antibiotics have been used for GI infections, particularly those caused by bacteria resistant to other drugs.[13] The quinolones may also be used as combination therapy in animals with mixed intraabdominal infections.[14] Fluoroquinolones are used as systemic therapy for deep pyoderma, other soft tissue infections, and bacterial osteomyelitis.[10,15] Although fluoroquinolones have some efficacy against intracellular pathogens, a study evaluating enrofloxacin for *Mycoplasma haemofelis* found that a therapeutic effect was achieved only at levels associated with retinal toxicity. Enrofloxacin was not effective in treating *Ehrlichia* infections in experimentally infected dogs.[16,17]

* Off-label use.

197.9 ADMINISTRATION AND DRUG INTERACTIONS

Although all of the fluoroquinolones marketed for small animals are labeled for oral use, both enrofloxacin and ciprofloxacin have been administered off-label intravenously in experimental dogs. Dosing recommendations for fluoroquinolone antibiotics in dogs and cats can be found in Table 197-2. When given intravenously, fluoroquinolone antibiotics should be diluted and administered slowly. Side effects of rapid intravenous administration may include seizures and neurologic sequelae. In addition, intravenous administration of these drugs may cause local tissue reactions or thrombophlebitis. Concurrent administration of antacids decreases absorption, so oral fluoroquinolones should be given 2 hours before or 6 hours after oral antacids. In addition, some fluoroquinolones may inhibit the metabolism of theophylline and aminophylline, leading to toxicity from elevated levels of methylxanthines. Fluoroquinolone antibiotics may decrease the efficacy of concurrently administered phenytoin.

197.10 ADVERSE EFFECTS

Fluoroquinolone antibiotics are generally well tolerated. The predominant side effects include vomiting, diarrhea, nausea, and abdominal discomfort. These effects are typically mild and dosage related. Discontinuation of the drug or dose reduction often results in relief of clinical signs. Seizures, tremors, and abnormal electroencephalographic findings have been reported in dogs and cats after administration of fluoroquinolones.[1]

Fluoroquinolones directly inhibit γ-aminobutyric acid receptors and stimulate N-methyl-D-aspartate receptors in the central nervous system. These effects appear to be exacerbated in the presence of nonsteroidal antiinflammatory medications, theophylline, and other drugs that interfere with the metabolism of fluoroquinolones.[12] Fluoroquinolones inhibit cytochrome P-450 enzyme metabolism. Occasionally animals may exhibit increases in hepatic transaminase values or liver function tests.[18] Therefore these antibiotics should be used with caution when administered with other hepatotoxic medications or in animals with hepatic disease.

Renal lesions resulting from precipitation of crystals in the tubular lumens of animals and humans receiving high or supratherapeutic doses of fluoroquinolones have been seen rarely.[19] Fluoroquinolone use has been associated with cartilaginous defects in juvenile animals and humans.[20] The pathogenesis of quinolone-induced cartilage damage is multifactorial. Proposed mechanisms include inhibition of proteoglycan synthesis, chelation of magnesium, and inhibition of mitochondrial dehydrogenase activity. In humans, the damage appears to be reversible with discontinuation of therapy. In one study in veterinary medicine, cartilage defects in young dogs were exacerbated by exercise and prevented by exercise restriction.[21] Fluoroquinolone antibiotics are contraindicated in young, growing dogs between the ages of 2 to 8 months, and up to 18 months in large breed dogs.

Rapid intravenous injection of fluoroquinolones produced dose-related elevations in plasma histamine level in one study in anesthetized dogs. Another study evaluating cardiovascular variables in anesthetized dogs receiving marbofloxacin found that at high cumulative dosages (≥12 mg/kg) dogs developed arterial hypotension, decrease in heart rate, and prolongation of the QT interval.[22] A prolonged QT interval and predisposition to torsades des points has been reported in human medicine. Reports of reversible blindness associated with fluoroquinolone use were first made in the early 1990s in human medicine. Since 1992, several documented cases of blindness have been associated with fluoroquinolone use in cats. Most cats received dosages at the upper limit or above the labeled daily dosage of 5 mg/kg q24h, suggesting that this toxicity is dosage related rather than idiosyncratic.[23]

Histopathologically, these cats have evidence of retinal degeneration, with cell death most prominent in the photoreceptor and the outer nuclear cell layers. Most cats have irreversible vision loss. This reaction has been seen most commonly secondary to enrofloxacin but also has been reported with orbifloxacin and marbofloxacin.[23] Reports of fetal toxicity and photosensitization in veterinary medicine are infrequent. Other side effects of fluoroquinolone use in humans, such as abnormalities in glycemic control, have not yet been investigated in veterinary medicine.

197.11 SUGGESTED FURTHER READING*

DL Frazier, L Thompson, A Trettien, et al.: Comparison of fluoroquinolone pharmacokinetic parameters after treatment with marbofloxacin, enrofloxacin, and difloxacin in dogs. *J Vet Pharmacol Ther*. **23**, 2000, 293, *A study that evaluated the concentration of three fluoroquinolone antibiotics in various tissues after the administration of once daily dosing for 5 consecutive days in dogs; in addition, a comparison of the pharmacokinetics and pharmacodynamics of the drugs*.

CE Greene, ADJ Watson: Antibacterial chemotherapy. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. ed 3, 2006, Saunders, St Louis, *A book that contains in-depth summaries of a variety of infectious diseases encountered in small animal veterinary practice, including description of etiologic agents, clinical course, and therapeutic recommendations. An excellent resource book for the small animal practitioner*.

C Wiebe, D Pharm, P Hamilton: Fluoroquinolone-induced retinal degeneration in cats. *J Am Vet Med Assoc*. **221**, 2002, 1568, *An article that provides a summary of veterinary case reports suggesting an association between fluoroquinolone administration and retinal degeneration in cats. Also summarizes postapproval safety studies conducted by the manufacturer for the enrofloxacin, orbifloxacin, and marbofloxacin and discusses possible mechanisms of fluoroquinolone-induced retinal degeneration*.

* See the CD-ROM for a complete list of references

198 Chapter 198 Macrolides

Scott P. Shaw, DVM, DACVECC

198.1 KEY POINTS

- Macrolides are concentrated in macrophages, resulting in high drug levels at the site of infection.
- Macrolides exhibit high levels of efficacy against gram-positive organisms and moderate efficacy against anaerobic organisms.

198.2 INTRODUCTION

Macrolides represent a large group of similar compounds that are all products of *Streptomyces* spp. Biochemically they are characterized by a macrocyclic lactone ring attached to one or more sugar moieties. Macrolides with the greatest clinical efficacy generally are derived from erythromycin. It should be noted that azithromycin is not technically a macrolide, but rather an azalide. It generally is grouped with the macrolides because it shares most of their properties.

198.3 MECHANISM OF ACTION

All macrolides work by reversibly binding the 50s ribosome. This results in suppression of ribonucleic acid–dependent protein synthesis. Macrolides are bacteriostatic at clinical concentrations. They are particularly effective against gram-positive organisms and *Mycoplasma* spp. In addition, they have fair efficacy against anaerobic organisms. Many macrolides are actively concentrated in macrophages. This can result in very high drug concentrations at the site of infection.[1]

198.4 PHARMACOLOGY

In general, macrolides are characterized by low serum concentrations and large volumes of distribution. They are concentrated in tissues including the lung, heart, and macrophages. Newer macrolides such as azithromycin have high oral bioavailability (40% to 60%) and long half-lives. The main route of excretion is through bile and the intestinal tract.[2]

198.5 RESISTANCE

Resistance to macrolides can develop rather quickly. This can occur through a one-step mutation that confers high levels of resistance. This type of resistance can be unstable, but it can develop during treatment. Most low-level resistance is caused by an efflux pump that actively excretes the drug out of the cell. Widespread resistance typically occurs when a gene coding for the methylation of the drug's target site is transferred via a plasmid.[3]

198.6 SELECTED MACROLIDES

198.6.1 Erythromycin

Erythromycin is available for both enteral and parenteral administration. When given enterally it is subject to rapid degradation by gastric acid. As a result, tablets and capsules typically are protected by an enteric coating. It is important that tablets not be crushed or divided, because this can result in inactivation of the drug before it is absorbed.[2]

Dosage-related gastrointestinal (GI) side effects are encountered frequently. These are believed to be secondary to the drug's effects on smooth muscle. The parenteral form can cause tissue irritation at the site of injection.[1]

Erythromycin is the drug of choice for treatment of *Campylobacter jejuni*. It can also be used as an alternative to penicillin in penicillin-sensitive animals. In small animals, it is employed most commonly in those with liver failure for its prokinetic effects on GI smooth muscle and ability to limit overgrowth of ammonia-producing organisms within the GI tract.[2]

198.6.2 Azithromycin

Azithromycin has greater activity against gram-negative organisms than the other members of the macrolide family. It is effective against *Bartonella, Borrelia, Campylobacter, Chlamydia, Leptospira,* and *Mycoplasma*. It is more stable in acid and as a result has a high oral bioavailability. Azithromycin appears to be taken up rapidly by tissues, then released slowly. Tissue concentrations are generally 10 to 100 times those achieved in serum, and the drug can be concentrated 200 to 500 times in macrophages. This high level of drug in macrophages may not always be advantageous, because it can suppress phagocytic activity. Azithromycin does not exhibit any effect on GI smooth muscle. As a result GI side effects are uncommon.[1]

Azithromycin commonly is employed by veterinarians to treat severe respiratory infections. It can be highly effective in resolving chronic difficult-to-resolve cases of pneumonia, particularly those secondary to *Bordetella* infection. Care should be taken when employing azithromycin as a sole agent because of the limitations on its gram-negative spectrum and because resistance is a growing problem. In general azithromycin should be reserved as a second-line or third-line agent.

198.7 SUGGESTED FURTHER READING*

D Boothe: In *Small animal clinical pharmacology and therapeutics*. 2001, Saunders, Philadelphia, *Text that provides an excellent reference for everyday use, covering both basic pharmacology and providing practical guidance for choosing appropriate antimicrobials in clinical patients*.

* See the CD-ROM for a complete list of references

199 Chapter 199 Antifungal Therapy

Marie E. Kerl, DVM, DACVIM, DACVECC

199.1 KEY POINTS

- Antifungal drug therapy for systemic fungal infections requires administration for months to resolve disease.
- Amphotericin antifungal drugs must be administered by systemic injection and cause significant nephrotoxicity.
- Azole-type antifungals are administered orally and cause varying degrees of hepatotoxicity.

199.2 INTRODUCTION

Limited classes of drugs are available to treat fungal infections. Antifungal drugs used to treat systemic fungal infections include polyene antibiotics and azole derivatives. Antifungal drugs are costly, require long-term administration, and have relatively high toxicity rates. In immunodeficient animals, definitive cure with any therapy is difficult or impossible. This chapter will review commonly available drugs and provide dosing information to treat various systemic fungal infections in dogs and cats (see Chapter 110, Fungal Infections).

199.3 CLASSES OF ANTIFUNGAL DRUGS

199.3.1 Polyene Antibiotics

Polyene antibiotics used to treat systemic mycoses include amphotericin B (AMB) and lipid-complexed AMB. AMB is produced by the microorganism *Streptomyces nodosus* and is considered the gold standard for antifungal therapy.[1,2] Parenteral administration is required because gastrointestinal absorption is poor. Following intravenous (IV) administration, AMB is protein bound and then redistributes from the blood to the tissues. Metabolic pathways of AMB are poorly understood. Biphasic elimination occurs, with an initial half-life of 2 to 4 days and a terminal half-life of 15 days.[3] Only a small amount undergoes renal and biliary elimination, and central nervous system (CNS) penetration is poor. AMB binds to ergosterol in fungal cell membranes, increasing membrane permeability to cause cell death. There is also affinity for cholesterol found in mammalian cell membranes, which explains its toxic effects. Parenteral administration might make AMB a more desirable treatment than oral drugs in animals with severe gastrointestinal fungal disease because they may absorb oral drugs poorly.

Dosing protocols for AMB include intermittent administration until a cumulative dosage has been achieved, with interruption of therapy in the event of azotemia. Cats typically receive lower intermittent and cumulative dosages than dogs (Table 199-1). To reduce nephrotoxicity, AMB usually is infused in 5% dextrose and administered IV over 1 to 5 hours. Blood urea nitrogen and urine sediment evaluation should be measured before each dose. Identification of tubular casts in urine sediment is an earlier indicator of ongoing renal tubular damage than serum biochemical test results, and the treatment regimen should be altered if casts are identified. If blood urea nitrogen exceeds 50 mg/dl, the drug should be discontinued until azotemia resolves.[2] Administration of 0.9%

saline IV before giving AMB decreases the incidence of nephrotoxicity in people.[4] Medications with known nephrotoxicity should not be given concurrently with AMB.

Lipid-complexed AMB drugs are newer preparations and have the advantage of being less nephrotoxic than AMB, even when administered at higher cumulative dosages. Formulations that are approved for use in people include AMB-lipid complex (ABLC, Abelcet), AMB colloidal dispersion (Amphotec), and liposome-encapsulated AMB (AmBisome).[1] All of these compounds require parenteral administration. Few head-to-head comparisons of these drug preparations make comparisons of efficacy difficult.[5] Abelcet has been used successfully to treat blastomycosis in dogs.[6] The main disadvantage of these drugs is a significantly greater expense compared with AMB.

Table 199-1 Drug Dosages to Treat Common Systemic Fungal Infections in Dogs and Cats

Infection	Species	AMB[*]	Liposomal AMB	Flucytosine[†]	Ketoconazole[‡]	Itraconazole Flucytosine[‡]	Fluconazole
Blastomycosis	Dog	0.5 mg/kg IV 3×/wk Cumulative dosage: 4 to 6 mg/kg	1 mg/kg IV 3×/wk Cumulative dosage: 12 mg/kg	—	5 to 15 mg/kg PO q12h for at least 3 months, with AMB initially	5 mg/kg PO q12 h for first 5 days, then q24 h for 60 to 90 days, or 30 days beyond resolution	5 mg/kg PO q12 h for at least 60 days, or 30 days beyond resolution
	Cat	0.25 mg/kg IV 3×/wk Cumulative dosage: 4 mg/kg	—	—	10 mg/kg PO q12 h for at least 3 months, with AMB initially	5 mg/kg PO q12 h for 60 to 90 days, or 30 days beyond resolution	—
Histoplasmosis	Dog	0.25 to 0.5 mg/kg IV 3×/wk Cumulative dosage: 5 to10 mg/kg	—	—	10 mg/kg PO q12-24 h for at least 3 months, or 30 days beyond resolution	5 mg/kg PO q12 h for 4 to 6 months, or 60 days beyond resolution	2.5 to 5 mg/kg PO q12-24 h for 4 to 6 months, or 30 days beyond resolution
	Cat	0.25 to 0.5 mg/kg IV 3×/wk Cumulative dosage: 4 to 8 mg/kg	—	—	See caninerecommendations	See canine recommendations	See canine recommendations
Cryptococcosis	Dog	0.25 to 0.5 mg/kg IV 3×/wk Cumulative dosage: 4 to 10 mg/kg	1 mg/kg IV 3×/wk Cumulative dosage: 8 to 12 mg/kg	50 mg/kg PO q6-8h for 1 to 12 months	10 mg/kg q12-24 h following AMB and flucytosine, for 4 to 6 months	—	5 to15 mg/kg PO q12-24h for 6 to10 months, or 30 days beyond resolution
	Cat	0.1 to 0.5 mg/kg IV Or 0.5 to 0.8 mg/kg SC3×/wk Cumulative dosage: 4 to 10 mg/kg	—	25 to 50 mg/kg PO q6-12 h for 1 to 9 months	See canine recommendations	5 to 10 mg/kg PO q12h, or 20 mg/kg q24h for 6 to 10 months, or 30 days beyond resolution	See canine recommendations
Coccidioidomycosis	Dog	0.4 to 0.5 mg/kg IV 3×/wk Cumulative dosage: 8 to11 mg/kg	—	—	5 to 10 mg/kg PO q12 h for 8 to 12 months	5 mg/kg PO q12h up to 12 months	5 mg/kg PO q12 h up to 12 months
	Cat		—	—	50 mg per cat PO q12-24h up to 12 months	25 to 50 mg per cat PO q12-24h up to 12 months	25 to 50 mg per cat PO q12-24 h up to 12 months

From Kerl ME: Update on fungal diseases, *Vet Clin North Am Small Anim Pract* 33:721, 2003.

AMB, Amphotericin B; *IV,* intravenous; *PO,* per os; *SC,* subcutaneous.

* Monitor for nephrotoxicity.

† Combine with AMB treatment.

† Administer with food.

199.3.2 Azole Antifungals

The azole antifungal drugs inhibit the fungal P-450 enzyme necessary for development of ergosterol in fungal cell walls.[5] Itraconazole and fluconazole are newer drugs than ketoconazole with fewer side effects and are mainstays of therapy for veterinary systemic mycoses. These drugs are administered orally, with peak plasma concentrations occurring within 6 to 14 days. Ketoconazole and itraconazole are weak bases, lipophilic, and protein bound. Absorption is improved in an acid environment, and uptake may be impaired with concurrent use of antacids or histamine-2 receptor antagonists. Distribution occurs through most tissues except the CNS and urine. Fluconazole is minimally protein bound, highly water soluble, and crosses the blood-brain, blood-ocular, and blood-prostate barriers.[1,2] Drugs that are metabolized by the hepatic P-450 enzyme system (especially histamine-2 receptor antagonists) may delay metabolism of azole antifungals, especially ketoconazole, thereby resulting in higher plasma drug concentrations.[3]

Ketoconazole has been effective as a sole agent for treatment of systemic mycoses, but it is less effective than AMB. In serious systemic fungal infections, combination therapy with AMB and ketoconazole may allow reduced dosage and toxicity while maintaining efficacy. Side effects of ketoconazole therapy include GI upset, which may be reduced by administering with meals and dividing the dosage into multiple smaller doses daily. Of the commonly used azole antibiotics, ketoconazole is the most likely to induce mammalian P-450 enzyme systems to cause elevations in hepatic transaminases and alkaline phosphatase. Clinical hepatitis that may be fatal has been recognized.[1,3]

Itraconazole has been effective as a sole agent in blastomycosis, histoplasmosis, coccidioidomycosis, and cryptococcosis. Absorption is most consistent when administered with a meal. Itraconazole more selectively inhibits fungal P-450 enzymes than mammalian P-450 enzymes to limit hepatotoxicity. Mild hepatic transaminase elevation can still occur.[1,7]

Cutaneous reactions consisting of localized ulcerative dermatitis and vasculitis occur in a small percentage of dogs receiving itraconazole; dermal lesions resolve following discontinuation of therapy.[2] Itraconazole is available from many veterinary formulating pharmacies at a reduced cost compared with the brand name pharmaceutical preparation (Sporanox); however, efficacy of generic preparations has not been proven. The commercially available liquid form may be better absorbed orally, especially in cats.[8] An IV injectable form is available for treatment of severe, resistant fungal infections.[2]

Fluconazole crosses the blood-brain barrier better than the other azole antifungals and has more consistent oral absorption on an empty stomach. Therefore it is indicated for CNS involvement in systemic mycoses and for anorexic animals. Fluconazole has been used successfully to treat cryptococcosis in cats.[9] Fluconazole is metabolized minimally and is excreted mostly in an intact form in the urine. The dosage of fluconazole should be reduced in animals with decreased glomerular filtration rates.[2]

Voriconazole is a synthetic derivative of fluconazole that has been approved by the US Food and Drug Administration and is available to veterinarians. It is licensed for use in humans to treat invasive aspergillosis and oropharyngeal candidiasis in immunocompromised patients. Cost is prohibitive for routine use, and there are no published reports of use in dogs or cats.[1,2]

199.3.3 Flucytosine

Flucytosine (Ancobon) is a pyrimidine originally developed as an antineoplastic agent for humans. Although it was ineffective for treating cancer, it has some antifungal activity. The drug is taken up by the fungal cell and converted to 5-fluorouracil, which then interferes with deoxyribonucleic acid and protein synthesis. Drug resistance develops rapidly. It was used in combination with AMB for cryptococcosis before newer azole antifungal drugs became available.[10] Toxicities include dermal eruptions in dogs and hematologic changes at high dosages in humans.[5,10]

199.4 RECOMMENDATIONS FOR SPECIFIC FUNGAL INFECTIONS

199.4.1 Blastomycosis

Itraconazole is the treatment of choice for blastomycosis because of efficacy, safety, and convenience of administration. In a study of 112 dogs comparing itraconazole with historical controls treated with AMB, response and recurrence rates were similar among all groups.[11] Other options include ketoconazole, AMB, and lipid-complexed AMB. Ketoconazole is much less effective than itraconazole, with lower response rates, higher relapse rates, and longer treatment periods.[2] AMB has been used successfully for blastomycosis. Drawbacks of AMB include parenteral administration and risk of nephrotoxicity. Lipid-complexed AMB is effective for blastomycosis in dogs, with less risk of nephrotoxicity than AMB.[6] Combinations of AMB and itraconazole or ketoconazole may be used in cases of severe respiratory infection.[2] Refer to Table 199-1 for dosage recommendations.

199.4.2 Histoplasmosis

Itraconazole is the drug of choice for histoplasmosis.[2] GI drug absorption has not been predicted accurately in animals with GI or disseminated histoplasmosis. Fluconazole has better penetration into the eye and CNS than itraconazole, but this drug has not been studied extensively for histoplasmosis in dogs and cats, and response to itraconazole has been reported in cats with CNS and ocular infection.[7] Fluconazole can be considered with CNS involvement or in cases refractory to AMB and itraconazole. With severe GI or disseminated disease, parenteral AMB combined with itraconazole, or high-dose itraconazole, has been recommended for more rapid control of fungal disease.[8]

Treatment should be continued for at least 60 days, or until 1 month following resolution of clinical signs. Complete resolution with GI or disseminated histoplasmosis is challenging to determine, and serologic antibody testing cannot help to identify response to therapy. Animals that relapse after discontinuation of therapy should resume antifungal drug treatment. Refer to Table 199-1 for dosage recommendations.

199.4.3 Coccidioidomycosis

Coccidioidomycosis is difficult to cure compared with other fungal infections, with some cases requiring lifelong therapy. Commonly recommended treatments for dogs and cats include azole antibiotics and AMB; however, controlled therapeutic trials are lacking. Respiratory infection can be cleared spontaneously by the host immune response; therefore debate exists over the criteria indicated to initiate prolonged therapy with expensive and potentially toxic medication.[2,12] Early initiation of therapy in primary respiratory coccidioidomycosis may be appropriate because dissemination is possible. The decision to discontinue therapy is based on resolution of clinical signs and resolution of elevated titers; complement fixation (CF) titers may become negative or may remain positive at 1:2 to 1:4.

Ketoconazole has traditionally been the treatment of choice for coccidioidomycosis. Serologic testing should be repeated within 4 to 6 weeks of initiation of therapy. If the titer is increasing or clinical signs deteriorating, alternative therapy should be chosen. Prolonged treatment (8 to 12 months) may be needed.[12] Itraconazole is an alternative to ketoconazole with fewer side effects; however, efficacy remains undetermined for dogs and cats. AMB is indicated in animals that experience significant side effects with azole drugs. Liposome-encapsulated AMB formulations may have fewer side effects while retaining efficacy but have not been studied for this disease.[12]

Relapse is common after discontinuation of therapy, particularly in cats.[13] Duration of therapy is generally recommended for months. Decisions to discontinue therapy should be based on resolution of clinical signs and improvement of serologic test results. Positive CF test results are not unusual even with treatment; however, increasing titers can be interpreted as treatment failure or relapse following discontinuation of therapy.[12] Refer to Table 199-1 for dosage recommendations.

199.4.4 Cryptococcosis

A variety of protocols and regimens have been developed for cryptococcosis in dogs and cats; choice of therapy depends on available drugs, location of infection, and side effects. Itraconazole is the drug of choice for cryptococcosis in most cats because of the combination of efficacy and safety compared with other treatment regimens.[10] Ketoconazole has been shown to cure infection; however, inappetence occurs more frequently with ketoconazole than with itraconazole.[10,14]

Subcutaneous or intravenous AMB has been used with azole antifungals or flucytosine in serious CNS or disseminated feline and canine cryptococcosis.[2,10] Azole antifungal agents typically are administered for 8 to 10 months, but longer therapy could be required in certain individuals. Recommendations to discontinue therapy 1 month after resolution of clinical signs and decrease in antigen titer by two orders of magnitude or until negative have been proposed for cats.[10] Refer to Table 199-1 for dosage recommendations.

199.5 SUGGESTED FURTHER READING*

D Boothe: Treatment of fungal infections. In DM Boothe (Ed.): *Small animal clinical pharmacology and therapeutics*. ed 1, 2001, Saunders, Philadelphia, *This chapter provides a thorough review of the pharmacologic aspects of common antifungal chemotherapeutics.*

CE Greene: Antifungal chemotherapy. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. ed 3, 2006, Mosby, St Louis, *The definitive reference for small animal infectious disease. Chapter that provides a review of drugs used to treat fungal infections*.

DR Krawiec, BC McKrawiec, AR Twardock, et al.: Use of an amphotericin B lipid complex for treatment of blastomycosis in dogs. *J Am Vet Med Assoc*. **12**, 1996, 207, *An article that presents a prospective case series of dogs treated with liposome-encapsulated AMB, finding that higher dosages could be administered with reduced risk of nephrotoxicity*.

I Lu, E Dodds, J Perfect: New antifungal agents. *Semin Resp Infect*. **17**, 2002, 140, *Article that reviews newer antifungal agents and those being developed to treat fungal infections in humans*.

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* See the CD-ROM for a complete list of references

200 Chapter 200 Miscellaneous Antibiotics

Reid P. Groman, DVM, DACVIM

200.1 KEY POINTS

- With the emergence of resistant microorganisms and competition from newer antimicrobial agents, it is especially important to revisit and pursue rational approaches to the use of older antibiotics in small animals.
- Metronidazole, chloramphenicol (CHPC), tetracyclines, potentiated sulfonamides, aztreonam, vancomycin, polymyxins, clindamycin, and more recently developed antibiotics may prove useful in the treatment of various infections in small animal veterinary medicine.
- Metronidazole is predictably effective against obligate anaerobes. Self-limiting neurotoxicity is associated with high-dosage or long-term use.
- CHPC is a time-honored broad-spectrum antibiotic with additional activity against spirochetes, rickettsiae, chlamydiae, and *Mycoplasma* spp. Rare complications from human exposure to this drug have limited its use in animals.
- Doxycycline is more lipophilic and has better tissue penetration than tetracycline. It remains the drug of choice for Lyme disease and many rickettsial infections.
- Potentiated sulfonamides are useful agents for a variety of bacterial, protozoal, and opportunistic mycobacterial infections, although adverse reactions often limit their use.
- Aztreonam is primarily effective against gram-negative aerobic bacteria in humans, but veterinary applications have not been defined.
- Vancomycin is presently the last line of defense against multidrug-resistant gram-positive cocci in dogs and cats.
- Polymyxin E (colistin) may prove useful in the treatment of multidrug-reistant gram-negative infections in companion animals.
- Clindamycin has a broad spectrum of activity against most gram-positive cocci and is active against most anaerobic pathogens.
- Proper use of all antibiotics, including novel agents such as the streptogramins, oxazolidinones, tigecycline, and the cyclic lipopeptides, is increasingly important to curtail the evolution of antimicrobial resistance.

200.2 INTRODUCTION

One of the greatest accomplishments of modern medicine has been the development of antibiotics for potentially fatal infections. However, this has inevitably been followed by the acquisition of resistance toward their antibacterial activity.[1] Unfortunately, the past two decades have seen a marked decline in the discovery and development of novel antibiotics and a remarkable increase in resistance to those in use. In particular, there is substantial worldwide concern with the mounting prevalence of infections caused by multidrug resistant (MDR) gram-positive and gram-negative bacteria. Veterinary clinicians and microbiologists have been forced to reappraise the value of both relatively older antibiotics and some more novel agents for the treatment of serious bacterial infections.

200.3 METRONIDAZOLE

The spectrum of metronidazole is limited to anaerobic bacteria and some protozoa. Although its mechanism of action is not entirely clear, the parent drug's nitro group is reduced by an electron transport protein in anaerobic bacteria. The reduced drug causes strand breaks in the DNA. Mammalian cells are unharmed because they lack enzymes to reduce the nitro group of these agents. Metronidazole diffuses well into tissues and body fluids, including cerebrospinal fluid, bile, and abscesses. Effective tissue penetration and consistent bactericidal activity make metronidazole useful for severe anaerobic infections, including intraabdominal sepsis, endocarditis, and osteomyelitis. Other antimicrobial agents should be used in combination with metronidazole if facultative and aerobic pathogens are suspected. The beneficial effects of metronidazole are often attributed to its antiinflammatory properties, in addition to its antibacterial activity. Notably, the immunomodulatory effects of metronidazole are believed to be in part responsible for amelioration of clinical signs in companion animals with inflammatory bowel disease and gingivostomatitis.

Seizures, cerebellar dysfunction, and other neuropathies have been reported with high dosages or long-term use of metronidazole. Although these untoward effects are generally self-limiting, complete recovery may take days to weeks. In general, the dosage should not exceed 30 mg/kg q24h for dogs and cats. Metronidazole should be given with particular caution in patients with underlying neurologic disorders. Intravenous diazepam administration may lessen the duration and severity of neurologic signs in affected dogs.

200.4 CHLORAMPHENICOL

Chloramphenicol (CHPC) was the first truly broad-spectrum antibiotic discovered. After initial widespread use, the agent was largely abandoned in developed countries following concerns over toxicity and the availability of antibiotics perceived safer and with a similar spectrum.[2] The rise in antibiotic resistance to many agents in the 1990s has prompted a reevaluation of CHPC in human and veterinary medicine.[2]

CHPC inhibits protein synthesis in bacteria. It acts primarily on the 50s ribosomal subunit and suppresses the activity of peptidyl transferase, an enzyme that catalyzes peptide bond formation.[2] Depending on the pathogen, the effect of CHPC may be bactericidal or bacteriostatic.[2] CHPC is active against gram-positive and gram-negative 845 846 aerobic and anaerobic bacteria, as well as spirochetes, rickettsiae, chlamydiae, and *Mycoplasma* spp.[1,2] It is often effective for treating *Salmonella* and *Escherichia* infections in the GI tract.[1] Its spectrum generally does not include *Pseudomonas aeruginosa*. [1] CHPC is not predictably active against most *Ehrlichia* spp. Although its lipid solubility permits it to cross the blood-brain barrier, its efficacy for treating central nervous system (CNS) infections is unpredictable.[1]

The intravenous form, CHPC sodium succinate, is a prodrug hydrolyzed to active CHPC, producing serum levels 70% of those obtained with oral dosing in humans. Metabolism takes place mainly in the liver, and inactive conjugated CHPC is excreted by the kidneys. CHPC should be used with caution in patients with liver disease. Although only a small fraction of active CHPC appears unchanged in the urine, adequate concentrations are achieved to treat many urinary tract infections (in the absence of advanced renal disease).[1]

Reversible bone marrow suppression and GI upset are observed occasionally in small animals, particularly with high dosages or prolonged treatment. Cats appear to be particularly susceptible, and routine blood monitoring is advised in this species, especially if therapy extends beyond 2 weeks.[3] Owners should be warned that exposure to CHPC may pose a health risk. Although extremely rare, CHPC exposure through aerosolization or oral intake is associated with fatal bone marrow aplasia in humans.[2] Contact with mucosal surfaces is required for this severe reaction. Oral veterinary preparations are film coated, reducing the possibility of contact with active drug. Thus these uncommon reactions are essentially avoidable for caregivers.

Until recently, parenteral administration of CHPC was all but abandoned in human medicine. Its use had diminished in dogs and cats, as well. However, problematic organisms, notably MDR enterococci and methicillin-resistant *Staphylococcus aureus* (MRSA), often retain in vitro susceptibility to CHPC. Thus it may serve as a viable treatment option for these infections.[2] It is rarely administered empirically to cats or dogs, and it should be prescribed appropriately based on culture and susceptibility data.

200.5 TETRACYCLINES

The tetracyclines are used to treat a variety of infections, including pneumonia and soft-tissue and urinary tract infections. This drug class includes tetracycline, oxytetracycline, doxycycline, and minocycline. The tetracyclines generally are considered bacteriostatic. They bind primarily to the 30s subunits of bacterial ribosomes and inhibit protein synthesis.[4]

Among the drugs in this group, doxycycline is used more frequently in companion animals, particularly for treating tick-borne diseases or when parenteral therapy is warranted.[3] Doxycycline is highly lipophilic, has excellent tissue penetration, is inexpensive, and has a broad spectrum of activity, including many gram-positive, gram-negative, aerobic, and anaerobic bacteria, *Mycoplasma* spp, chlamydiae, rickettsiae, spirochetes, some protozoa, and select mycobacteria.[1,4] It is the drug of choice for treating Lyme disease and most *Ehrlichiae* infections. It is generally very effective for *Leptospira* spp and *Brucella* spp infections.[4] Doxycycline is effective against many strains of *Bordetella bronchiseptica. Bartonella* spp may also be treated with high-dosage doxycycline.

Unlike conventional tetracyclines, doxycycline is eliminated largely by nonrenal mechanisms and is considered safe for patients with renal failure.[4] Moreover, the half-life and serum levels of doxycycline are not altered in patients with renal failure.[4] Doxycycline has excellent tissue penetration, including the lung and bronchial secretions. Drug concentrations measured in most tissues generally are found to be higher than those in serum.[4] As with other tetracyclines, doxycycline possesses immunomodulatory and antiinflammatory effects that are independent of its antimicrobial properties.[1]

Most side effects are associated with oral administration and include GI upset and pill-induced esophageal erosion, particularly in cats.[1,4] The incidence of esophageal damage may be decreased by using coated forms of the drug and providing at least 10 ml of water or gruel to the patient in an upright position immediately following administration of the tablet or capsule.[3] There is limited evidence that doxycycline causes tooth discoloration or inhibits bone growth in juvenile patients. Although this is well documented with tetracycline (which is known to chelate divalent cations including calcium), it has not been substantiated for doxycycline. Rapid intravenous administration should be avoided.

200.6 POTENTIATED SULFONAMIDES

The sulfonamides, known widely as *sulfa drugs,* were the first antibacterial agents and paved the way for the antibiotic revolution in medicine.[5] Sulfonamide antibiotics such as sulfamethoxazole (SMX), sulfadiazine (SDZ), and sulfadimethoxine (SDM), potentiated by combination with either trimethoprim (TMP) or ormetoprim (OMP), inhibit steps in bacterial folic acid synthesis.[1] Folate is necessary for cells to synthesize nucleic acids, and in its absence cells are unable to divide. Folate is not synthesized in mammalian cells but is instead a dietary requirement.[5] This explains the selective toxicity of these agents to bacterial cells.

The potentiated sulfonamides have a broad spectrum of activity to include urinary, prostate, GI, CNS, bone, joint, skin, soft-tissue, and respiratory pathogens.[1,3,5,6] They are considered bactericidal against facultative gram-negative bacteria and staphylococci.[5] They have unpredictable activity against streptococci and no activity against enterococci or obligate anaerobes.[1] Many strains of *S. aureus, Escherichia coli, Proteus mirabilis, Enterobacter* spp, and *Salmonella enterica* are inhibited by the parenteral combination of SMX-TMP.[1,5] Oral preparations include SDZ-TMP, SMX-TMP, and SDM-OMP. There are no published reports of difference in efficacy between TMP-SDZ and TMP-SMX, although fewer side effects have been reported with the latter. The combination often retains activity against opportunistic gram-negative pathogens, including *Aeromonas* spp, *Burkholderia cepacia,* and *Acinetobacter* spp. However, *P. aeruginosa* is uniformly resistant.[1]

SMX-TMP is considered a first-line agent for nocardial infections.[1] SMX-TMP, alone or in combination with pyrimethamine, is an alternative treatment of toxoplasmosis in veterinary medicine.[3] Other protozoan and opportunistic mycobacterial infections are susceptible to the potentiated sulfonamides.[5] SMX-TMP is among the treatments of choice for *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia in dogs and humans.[5] In 846
vitro, SMX-TMP retains excellent activity against many MRSAs.[6,7] Because the potentiated sulfonamides are 847
distributed widely and maintain efficacy against some MDR-resistant *Staphylococcus* spp, their judicious use may serve as a model for use of older broad-spectrum antibiotics as bacterial resistance increases.[6]

Dosage-dependent adverse reactions associated with sulfonamide administration include anemia, proteinuria, crystalluria, and hematuria, and inhibition of thyroid hormone synthesis.[8] Effects on thyroid hormone function are most likely to manifest after 2 to 3 weeks of therapy and are reversible.[3] Idiosyncratic reactions, or sulfonamide hypersensitivity, may be seen after just 5 days of therapy at standard dosages.[8] Sulfonamide hypersensitivities may be observed after a standard course of therapy has been completed.[8] Signs in dogs can include fever, polyarthropathy, hepatotoxicity, skin eruptions, thrombocytopenia, and neutropenia.[8] Coombs-positive hemolytic anemia is observed less commonly than thrombocytopenia or neutropenia.

Idiosyncratic reactions are uncommon events and appear to be much less common in cats than dogs.[3] Larger dogs appear to be predisposed to sulfonamide-associated polyarthropathy. Sulfonamide-induced keratoconjunctivitis sicca is distinct from other adverse events in that the time to onset of signs is often months to years, rather than days to weeks.[8] Thus it is not clear if sulfonamide-induced keratoconjunctivitis sicca is idiosyncratic rather than dosage-dependent. Because the incidence is estimated to be 15%, and signs may be reversible if detected in short order, veterinarians are encouraged to evaluate Schirmer tear tests before and during therapy in dogs.

Dogs of Doberman Pinscher and Rottweiler lineage may be more sensitive than other breeds to sulfonamide reactions.[1] Sulfonamides should not be prescribed to dogs with underlying hepatic disease. OMP has been associated with some CNS effects in dogs, including anxiety and seizures.[3]

200.7 AZTREONAM

Aztreonam is the only monobactam on the market.[1] It has a significantly narrower spectrum than other β-lactams.[9] Specifically, its spectrum is limited to gram-negative aerobic bacteria.[9] It is effective for most members of the Enterobacteriaceae, including *E. coli, Enterobacter* spp, *Klebsiella* spp, *Proteus* spp, and *Serratia* spp. It is generally very effective for *P. aeruginosa,* but activity against *Acinetobacter* spp is limited.[9] Approximately 60% to 70% of aztreonam is renally excreted. It is available only for intravenous administration and has a favorable side effect profile. In human intensive care, it has been used for definitive treatment of nosocomial pneumonia and intraabdominal, soft-tissue, and other serious infections.[9] In polymicrobial infections or when used for empiric therapy, aztreonam must be given in combination with other antimicrobial agents that are effective against gram-positive and anaerobic species.

Appropriately, most commercial veterinary microbiology laboratories do not provide susceptibility data for aztreonam. Although pharmacokinetic studies have been performed, veterinary applications of aztreonam have not been defined. Its administration is justified only in patients with infections caused by pathogens uniquely susceptible to this agent or in patients that absolutely cannot tolerate aminoglycosides or other appropriate drugs used for gram-negative sepsis.[1]

200.8 VANCOMYCIN

Vancomycin, a glycopeptide bactericidal antibiotic, has been used in human medicine for over 40 years.[6] It works by binding to peptide precursors in the bacterial cell wall, preventing cross-linking of peptidoglycan side chains and thereby inhibiting cell wall synthesis.[1] Its spectrum is limited to most aerobic and anaerobic gram-positive organisms, including most isolates resistant to β-lactams.[1] Although vancomycin has been considered the last defense against gram-positive MDR pathogens in man, the late 1980s saw a rise in vancomycin-resistant bacteria, including vancomycin-resistant enterococci (VRE) and strains of *S. aureus*. [6]

Vancomycin is not absorbed across the intestinal wall, and it is limited to parenteral administration for all infections other than *Clostridium difficile*–associated diarrhea.[1] It is eliminated almost exclusively by the kidney, and dosage is adjusted in human patients with renal dysfunction. Vancomycin-associated renal impairment is reported, although it is infrequent and generally mild.[1] However, vancomycin may potentiate aminoglycoside nephrotoxicity. Optimal dosing regimens and the need for therapeutic drug monitoring both remain unresolved in human hospitals. The poor penetration of vancomycin into solid organs in patients with sepsis may preclude its use in disease states such as pneumonia.

Vancomycin use has increased significantly over the past 25 years, and it remains the workhorse agent for β-lactam–resistant staphylococcal and enterococcal infections in most human hospitals. The increasing number of vancomycin-resistant enterococcal and staphylococcal infections is an ominous trend in human health care.[10] It is a drug of last resort in veterinary medicine and is used only for highly resistant strains of *Staphylococcus* spp and *Enterococcus* spp. Because reports of vancomycin-resistant gram-positive pathogens in veterinary medicine are rare, and because of the emergence of vancomycin-resistant pathogens in humans, this drug ideally is kept in reserve and is never prescribed empirically to companion animals.

200.9 POLYMYXINS

Polymyxins B and E have a broad spectrum of activity that includes virtually all gram-negative bacteria. In addition to their bactericidal properties, polymyxins bind to and neutralize endotoxin through direct molecular interactions with the lipid A region. Although polymyxin B is still used as a component of topical preparations, parenterally administered polymyxin E (colistin) has been used little since the early 1980s because of the perceived high incidence of drug-related neurotoxicity and nephrotoxicity.[1] However, the mounting prevalence of infections caused by MDR bacteria such as *P. aeruginosa, Acinetobacter baumannii,* and *Stenotrophomonas maltophilia* has prompted clinicians and microbiologists to reappraise the clinical value of colistin.[11] Additionally, data from more recent literature suggest that colistin is associated with less severe toxicity than was reported in the older literature.[11]

The mechanism of action of polymyxins is not clear. They are cationic detergents and are thought to interact with the phospholipids of bacterial cell membranes, thereby leading to increased cell wall permeability and cell death. Some data suggest that colistin may be used safely and effectively in dogs.[12]

200.10 CLINDAMYCIN

The only lincosamide available in the United States is clindamycin.[1] Clindamycin binds to the 50s ribosomal subunit and inhibits protein synthesis in susceptible bacteria.[1] It shares the gram-positive coccal spectrum of erythromycin but is more active (in some cases showing bactericidal activity) against susceptible staphylococci, including some MRSAs, as well as toxoplasmosis, neosporosis, hepatozoonosis, and *Babesia* spp. Despite increasing resistance, clindamycin remains useful for most anaerobic infections. It has no clinically significant activity against facultative gram-negative enteric bacilli.[1] Clindamycin is recommended for use in a variety of skin, soft-tissue, respiratory, and bone infections. It is widely distributed in body tissues and fluids, including bile, prostatic fluid, and bone.[1] Although clindamycin notably achieves high intracellular concentration, it does not have enhanced activity against obligate intracellular pathogens; this is likely because the subcellular location of the antibiotic does not match that of the organism. Administered at recommended dosages, adverse effects associated with clindamycin in dogs and cats is infrequent.

200.11 NEWER AGENTS FOR MULTIDRUG-RESISTANT GRAM-POSITIVE COCCI

The incidence of serious gram-positive infections is increasing at an accelerated rate.[10,13] Resistant strains of *Enterococcus* spp and *Staphylococcus* spp are responsible for a substantial part of this disturbing trend (see Chapter 108, Gram-positive Infections).[13] Resistance to β-lactams and other agents has resulted in the increasing use of glycopeptides, such as vancomycin, for treating such infections in human medicine.[13] However, vancomycin-resistant enterococcus (VRE) and staphylococci are identified frequently in humans, although only rarely in veterinary patients.[10] In response to this challenge, a number of new antibiotics have been introduced, including the streptogramins (quinupristin-dalfopristin), the oxazolidinones (linezolid), tigecycline, and the cyclic lipopeptides (daptomycin).[1,10] Inclusion of these agents is warranted because they are now part of the pharmacologic armamentarium in human hospitals.[10,13]

The evidence that antimicrobial prescribing is the main driver of antimicrobial resistance is overwhelming, and avoiding unnecessary antimicrobial use is a plausible and easy-to-implement strategy to forestall the emergence of resistance in veterinary patients. None of the following agents have been evaluated adequately in companion animals with naturally occurring infections. Similarly, appropriate indications for prescribing these agents to dogs and cats do not yet exist.

200.11.1 Daptomycin

Daptomycin, a novel lipopeptide antibiotic, is bactericidal against a range of gram-positive isolates.[10] Its exact mechanism of action is not completely understood. It is thought to disrupt plasma membrane function, leading to the release of intracellular ions, specifically potassium, resulting in cell death.[13] It exhibits rapid, concentration-dependent bactericidal activity against susceptible isolates, including MRSA and vancomycin-resistant *Enterococcus faecium* (VREF).[13] It is used primarily for skin and soft-tissue infections caused by gram-positive bacteria, but is also used for complicated urinary tract infections caused by gram-positive pathogens. It is inactivated by surfactant and is not useful for treating pneumonia.[10] It is a relatively safe drug with very few reported adverse effects.[10] Daptomycin is eliminated by the kidneys, and dosage adjustments may be necessary in patients with renal dysfunction. Hepatic metabolism is limited. Daptomycin is available only for parenteral administration.[10]

200.11.2 Tigecycline

Tigecycline is one of the newest approved agents with activity against MDR gram-positive pathogens.[10] It is a synthetic analogue of tetracycline, with similar mechanism of action and antibacterial activity but improved ability to circumvent resistance. Tigecycline is used to treat complicated soft-tissue and intraabdominal infections in humans. It is active against many VRE strains and MRSA, as well as certain β-lactamase producing Enterobacteriaceae and anaerobes.

200.11.3 Quinupristin-Dalfopristin

Quinupristin-dalfopristin is a combination of two semisynthetic drugs.[10] Both have antibacterial capability individually but demonstrate synergistic activity when used in combination.[13] Both enter bacterial cells by diffusion and bind to different sites on ribosomes, resulting in irreversible inhibition of bacterial protein synthesis.[10] The drug is eliminated through the bile into feces. Quinupristin-dalfopristin has inhibitory activity against a broad spectrum of gram-positive bacteria, including MRSA, VREF, and many streptococci.[13] Quinupristin-dalfopristin also has shown synergy with other antibiotics.[1] Rifampin is synergistic with quinupristin-dalfopristin against MRSA and doxycycline against VREF in vitro.

Quinupristin-dalfopristin is indicated for serious infections caused by MDR, VREF, and MRSA, including soft-tissue infections, pneumonia, and bacteremia.[10] It is administered intravenously. Adverse events are reported infrequently but include myalgia, discomfort or thrombophlebitis at the site of injection, nausea, and increases in hepatic transaminase activity.[10] Although uncommon, resistance to quinupristin-dalfopristin has been encountered among VREF and MRSA in the United States.[1,10]

200.11.4 Linezolid

Linezolid is thought to inhibit the initiation phase of translation and thus interfere with protein synthesis.[13] In vitro studies have shown linezolid to be effective against many antibiotic-resistant gram-positive organisms, including MRSA and VRE. In addition, it is effective against gram-negative anaerobes, including *Bacteroides fragilis* and some mycobacteria.[13] Linezolid has been approved for the treatment of various gram-positive infections, including pneumonia, skin infections, and soft-tissue infections.[10] Linezolid is available for intravenous injection and oral administration.[10] Resistance has already been documented in both enterococci and staphylococci, and this may limit the use of this drug in the near future.[13] Human patients uncommonly 848 849 experience adverse events, such as nausea and self-limiting thrombocytopenia. Less common, but more serious, adverse effects include severe lactic acidosis and a disabling polyneuropathy.[10]

200.12 SUGGESTED FURTHER READING*

LE Asbel, ME Levison: Cephalosporins, carbapenems, and monobactams. *Infect Dis Clin North Am*. **14**, 2000, 435, *A concise review that includes the spectrum of activity, safety profile, limitations, and indications for aztreonam*.

CE Greene, DJ Watson: Antibacterial chemotherapy. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. ed 3, 2006, Saunders, St Louis, *A chapter that provides a detailed description of the historical background and clinical indications for both common and uncommon antibiotics in contemporary companion animal practice*.

DL Paterson: Clinical experience with recently approved antibiotics. *Curr Opin Pharmacol*. **6**, 2006, 486, *A critical and detailed discussion of the antibiotics employed to treat resistant gram-positive infections. Includes evaluation of randomized trials, novel resistance mechanisms, and adverse events*.

LA Trepanier: Idiosyncratic toxicity associated with potentiated sulfonamides in the dog. *J Vet Pharmacol Ther*. **27**, 2004, 129, *An outstanding review that includes both dosage-dependent and idiosyncratic adverse drug reactions associated with the potentiated sulfonamides. Includes frequency of occurrence, pathogenesis, and patient management. A must-read for clinicians who are uncertain about the untoward effects associated with these broad-spectrum agents*.

DW Wareham, P Wilson: Chloramphenicol in the twenty-first century. *Hosp Med*. **63**, 2002, 157, *A review article that includes the spectrum of activity, pharmacology, and contemporary clinical indications for this controversial antibiotic, including objective discussion of the risk of fatal bone marrow toxicity in humans*.

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* See the CD-ROM for a complete list of references

213 Chapter 213 Basic Mechanical Ventilation

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213.1 KEY POINTS

- Mechanical ventilation involves a machine that performs some or all of the work of breathing.
- The three indications for mechanical ventilation are severe hypoxemia despite therapy, severe hypoventilation despite therapy, and excessive respiratory effort.
- The goal of mechanical ventilation is to maintain adequate arterial blood gases (partial pressure of arterial carbon dioxide of 35 to 50 mm Hg, partial pressure of arterial oxygen of 80 to 120 mm Hg) with the least aggressive ventilator settings.
- Animals requiring mechanical ventilation suffer from either lung disease or neurologic or muscular dysfunction, or both.
- Animals with lung disease generally require more aggressive ventilator settings and have a poorer prognosis than animals with neuromuscular diseases.
- The “ideal” ventilator settings for a given patient can be determined only by trial and error.
- Positive end-expiratory pressure (PEEP) increases the oxygenating efficiency of diseased lungs by preventing alveolar collapse and reducing ventilator-induced lung injury. PEEP is also used to prevent atelectasis in animals requiring prolonged anesthesia and mechanical ventilation.
- Complications of mechanical ventilation include ventilator-associated pneumonia, ventilator-induced lung injury, and pneumothorax.

213.2 INTRODUCTION

A ventilator is a machine that performs some or all of the work of breathing. In veterinary medicine conventional positive-pressure ventilation is used most commonly. These machines utilize an increase in airway pressure to move gas into the lungs, in contrast to spontaneous breathing where airway pressure decreases below atmospheric pressure in order to generate the inspiratory phase of a breath.[1]

The respiratory function of the lungs is to oxygenate the arterial blood and remove carbon dioxide from the venous blood. Oxygenation refers to the movement of oxygen from the alveoli into the pulmonary capillaries and is primarily dependent on the surface area available for gas exchange and preservation of the delicate structure of the gas-exchange barrier.[2] Removal of carbon dioxide is primarily dependent on fresh gas movement into the alveoli; this process is ventilation. When managing patients on mechanical ventilation it is useful to think of oxygenation and ventilation as two separate processes.

213.3 VENTILATOR BREATH

Ventilator breaths can be spontaneous, assisted, or controlled. Spontaneous breaths occur when the patient determines the respiratory rate and tidal volume. Assisted breaths occur when the patient determines the respiratory rate but the tidal volume is generated by the machine. During controlled ventilation the machine determines both the respiratory rate and the tidal volume.[3]

The ventilator can generate a breath in one of two basic ways. It can deliver a preset tidal volume over a given inspiratory time (volume control), or the machine can provide and maintain a preset airway pressure for a given inspiratory time (pressure control). When delivering a volume-controlled breath, the peak airway pressure generated will be dependent on the preset tidal volume chosen and the compliance of the respiratory system. When a pressure-controlled breath is delivered, the tidal volume will depend on the preset airway pressure chosen and the compliance of the respiratory system.[1,3] The more basic machines tend to be either volume-control ventilators or pressure-control ventilators. More modern, advanced machines have the capability to generate several different breath types.

213.4 COMPLIANCE

Compliance is a measure of the distensibility of the lung and is defined as the change in lung volume for a given change in pressure.[2] A lung with high compliance will have a large increase in volume for a small pressure change, whereas low compliance would be characterized as requiring a large pressure change to create a small increase in volume. The normal, healthy lung is very compliant and, as a result, should require small airway pressures for adequate mechanical ventilation. In contrast, most pulmonary disease processes common to veterinary medicine will reduce pulmonary compliance and require higher airway pressures to adequately oxygenate and ventilate the patient.[1]

213.5 VENTILATOR SETTINGS

Every model has a different range of settings. The more modern and advanced the machine, the more options it will provide for the operator to manipulate the ventilator breath. Despite the apparent complexity of modern ventilators, only a few important ventilator settings, available on almost all machines, allow an effective ventilation protocol to be determined for a patient. These include respiratory rate, tidal volume, peak inspiratory pressure, inspiratory time, inspiratory-to-expiratory ratio, trigger sensitivity, and positive end-expiratory pressure (PEEP) (Table 213-1). The parameters that can be preset will depend on the type of ventilation being used. With volume-controlled ventilation the tidal volume or minute ventilation is preset by the operator and peak airway pressure is a dependent variable. Rather a peak airway pressure alarm limit is set to alert the operator of excessive airway pressures. If pressure control is used, the peak airway pressure is preset and tidal volume is a dependent variable. In some cases the parameters can be set directly or are indirectly determined by other settings. For example, the inspiratory-to-expiratory ratio can be preset directly on some ventilators, but with many machines it is the consequence of the inspiratory time and respiratory rate that is chosen by the operator.[1,3]

Table 213-1 Important Characteristics of a Ventilator Breath

Parameter	Definition
Fraction of inspired oxygen	Concentration of oxygen in the inhaled gas
Respiratory rate	Number of breaths per minute
Tidal volume	Volume of a single breath (ml)
Total minute ventilation	Total volume of breaths in a minute (ml) (V_T = TV × RR)
Inspiratory time	Duration of inspiration (sec)
Inspiratory-to-expiratory ratio	Duration of inspiration versus duration of expiration
Peak airway pressure	Peak pressure measured in the proximal airway (cm H_2O) during inspiration
Positive end-expiratory pressure	Positive airway pressure maintained during exhalation

RR, Respiratory rate; *TV*, tidal volume; V_T, total minute ventilation.

The trigger variable is the parameter that initiates inspiration, that is, how the ventilator determines when to deliver a breath. In animals that are not making respiratory efforts of their own, the trigger variable is time and is determined from the set respiratory rate. If the animal is making respiratory efforts, the trigger variable may be a change in airway pressure or gas flow in the circuit resulting from the patient attempting to initiate inspiration.[3,5] The trigger variable or sensitivity of the machine is set by the operator. An airway pressure drop of 2 cm H_2O or gas flow change of 2 L/min is an appropriate trigger sensitivity in most patients. It is important to always set the trigger sensitivity so that any genuine respiratory efforts made by the patient are detected by the machine and thus obvious to the operator. This is because an increase in respiratory rate may be the only mechanism by which a ventilated patient can indicate that there is a problem. The trigger variable can be too sensitive, such that nonrespiratory movement such as patient handling may initiate breaths. This should be avoided.

PEEP is available on many ventilators. If not provided by the machine, PEEP can be added by attaching a tube to the exhalation port of the ventilator. This can then be attached to a PEEP valve or the end of the tube can be submerged in the desired depth of water. PEEP, as the name suggests, maintains positive pressure during exhalation that prevents the lung from emptying completely. As a result the lung is “held” at a higher volume and pressure during exhalation.[1,3,4] PEEP is thought to increase the oxygenating efficiency of diseased lungs by recruiting previously collapsed alveoli, preventing further alveolar collapse, and reducing ventilator-induced lung injury.[1,3,5] The appropriate magnitude of PEEP depends on the severity of the lung disease and the clinical response of the patient. Initially it may be set between 2 and 5 cm H_2O and then titrated appropriately.

213.6

INDICATIONS FOR MECHANICAL VENTILATION

There are three main indications for mechanical ventilation: (1) severe hypoxemia despite therapy, (2) severe hypoventilation despite therapy, and (3) excessive respiratory effort.[1,5] Hypoxemia is defined as a partial pressure of arterial oxygen (PaO_2) of less than 80 mm Hg or a hemoglobin saturation (SpO_2) of less than 95%. A PaO_2 of less than 60 mm Hg or an SpO_2 of less than 90% is considered severe hypoxemia.

When patients have severe hypoxemia despite oxygen therapy and specific treatment of the primary disease, mechanical ventilation is indicated. Most of these animals have primary lung disease.[2,4] Inspired oxygen concentrations of greater than 60% for a prolonged period (24 to 48 hours) can lead to oxygen toxicity and subsequent pulmonary damage.[4] Therefore animals that require high concentrations of inspired oxygen for longer than 24 hours in order to achieve adequate oxygenation may also benefit from mechanical ventilation.[1]

Hypoventilation is defined as an elevation in the partial pressure of carbon dioxide ($PaCO_2$). Severe hypoventilation is defined as a $PaCO_2$ higher than 60 mmHg and is an indication for mechanical ventilation if the patient is unresponsive to therapy for the primary disease. Hypercapnia is a consequence of reduced effective alveolar ventilation. This may be due to increased dead space in a breathing circuit, upper airway obstruction, sedative overdose, or neuromuscular diseases that impair respiratory rate or chest wall movement.[2,4] Most patients with increased apparatus dead space, upper airway obstruction, or sedative overdoses will respond to therapy and will not require mechanical ventilation. Patients requiring ventilation in this category have neurologic, muscular, or neuromuscular disease processes such as brain disease, high cervical spinal cord disease, peripheral neuropathies, neuromuscular junction abnormalities, or primary myopathies. For simplicity, this group of disease processes will be considered neuromuscular diseases. Animals with brain disease may not tolerate small elevations in PCO_2, and mechanical ventilation may be indicated in these patients if the $PaCO_2$ is higher than 45 mm Hg.[4]

Animals with pulmonary disease may be able to maintain adequate oxygenation and ventilation by increasing respiratory effort. If respiratory effort is marked, patients can become exhausted and respiratory arrest can occur despite acceptable blood gas values. Intervention before arrest and initiation of mechanical ventilation may successfully stabilize these patients.[1,5] There are no objective measures of respiratory effort and impending fatigue; therefore this evaluation is one of clinical judgment.

213.7 APPROACH TO INITIATION OF MECHANICAL VENTILATION

Before initiating mechanical ventilation, appropriate machine setup and monitoring is required. The “ideal” ventilator settings for a given patient can be determined only by a process of trial and error. The initial ventilator settings are based on guidelines such as those given in Table 213-2. The operator should anticipate that animals with diseased lungs will require more aggressive ventilator settings and higher inspired oxygen concentrations than patients with neuromuscular disease.

Table 213-2 Suggested Initial Ventilator Settings

Ventilator Parameter	Initial Setting
Fraction of inspired oxygen	100%
Tidal volume	5 to 15 ml/kg
Respiratory rate	8 to 30 breaths/min
Minute ventilation	150 to 250 ml/kg
Peak inspiratory pressure	10 to 15 cm H_2O
Positive end-expiratory pressure	0 to 5 cm H_2O
Inspiratory time	≈1 second
Inspiratory-to-expiratory ratio	1:2
Inspiratory trigger	−1 to −2 cm H_2O

The machine should be turned on and tested with a rebreathing bag to be sure it is functioning properly. It is advisable to always start mechanical ventilation with 100% oxygen until appropriate ventilator function and patient stability can be confirmed. Following initial stabilization, the FiO_2 can be tailored appropriately. A separate source of 100% oxygen should be available at all times to provide manual ventilation in case of machine failure. Constant, intensive monitoring is essential for patients that are being ventilated, because they are completely dependent on their caregivers for survival. Problems may be masked by anesthesia or the primary disease process, and respiratory rate is no longer an indication of life; ventilators will easily ventilate a dead patient. Electrocardiography, core body temperature, arterial blood pressure, end-tidal carbon dioxide levels, and pulse oximetry monitoring ideally are provided for every ventilator patient. Arterial blood gas measurements are of great benefit for patients with pulmonary disease.

Patients will require general anesthesia in order to start mechanical ventilation unless they have severe neurologic deficits. Anesthesia is required both to secure the airway and to allow the patient to tolerate positive-pressure ventilation. Anesthesia induction should be rapid to allow immediate control of the airway and initiation of manual ventilation. All patients should receive high levels of inspired oxygen before and during induction. This is best provided by a tightly fitting face mask.

Following induction, maintenance anesthesia will be required. Inhalant anesthetics are not recommended, because most ventilator patients require long-term anesthesia (hours to days) and these agents raise serious personnel safety concerns. In addition, the inhalant anesthetics tend to have significant cardiovascular depressant effects that may be poorly tolerated by critically ill patients. The anesthetic protocol for maintaining ventilated patients will depend somewhat on the animal's clinical state. The combination of a benzodiazepine infusion with a second injectable agent may offer the advantages of balanced anesthesia. Anesthetic drug options are discussed further in Chapter 216, Care of the Ventilator Patient.

For animals that are unable to fight the ventilator, such as patients with respiratory paralysis, a temporary tracheostomy tube will allow the reduction or even removal of anesthetic agents and make neurologic evaluation and patient treatment simpler. Patients with normal neurologic function cannot be ventilated without anesthesia, even with a temporary tracheostomy tube.

Immediately after the patient is connected to the ventilator, the chest should be observed for appropriate movements. The ventilator settings should be adjusted if the chest wall movements appear excessive or inadequate. Auscultation should then be performed to confirm the presence of breath sounds bilaterally. If breath sounds are not audible bilaterally, endobronchial intubation may have occurred and the endotracheal tube should be retracted.

Auscultation over the larynx may help detect tracheal cuff leaks that can compromise the effectiveness of ventilation. Tracheal cuff pressures should not exceed 25 mm Hg; cuff pressure manometers help to prevent tracheal necrosis (i.e., Posey Cufflator). Parameters such as electrocardiography, pulse oximetry, end-tidal carbon dioxide level, and arterial blood pressure should then be evaluated and significant abnormalities addressed immediately. Once the patient is considered stable, arterial blood gases are evaluated while the animal is still receiving 100% oxygen, and the ventilator settings should be modified accordingly. In the absence of arterial blood gases, ventilator management is based on physical examination findings, venous PCO_2 levels, and pulse oximetry.

213.8 GOALS

The goal of mechanical ventilation is to maintain adequate arterial blood gas levels ($PaCO_2$ of 35 to 50 mm Hg, PaO_2 of 80 to 120 mm Hg) with the least aggressive ventilator settings. If blood gas values are inadequate using the initial ventilator settings, the machine is first inspected to ensure that it is functioning correctly. Patient-ventilator asynchrony needs to be resolved and significant issues such as pneumothorax or hyperthermia ruled out. The final option is to adjust the ventilator settings to improve oxygenation and ventilation accordingly. It is always simpler to make one change at a time in the ventilator settings so that the effect of each change can be interpreted accurately. Careful recording of ventilator settings with the concurrent arterial blood gas values, end-tidal carbon dioxide levels, and pulse oximetry readings is essential in evaluating and modifying the ventilator protocol.

213.8.1 Carbon Dioxide

Total minute ventilation (V_T) is equal to the product of the respiratory rate and the tidal volume. Carbon dioxide levels are controlled primarily by the alveolar minute ventilation ($V_A = V_T -$ dead-space volume). Dead space is any portion of the tidal volume that does not participate in gas exchange; increases in dead space result in decreases in effective alveolar ventilation and subsequent hypercapnia.[2,4] In small patients excess tubing length between the breathing circuit Y-piece and the animal's mouth can cause significant increases in dead space and a subsequent elevation in PCO_2. This may be a consequence of excessive endotracheal tube length, extension pieces, or monitoring devices connected to the end of the endotracheal tube. Endotracheal tube obstruction from kinking or the accumulation of airway secretions may also reduce the volume of effective alveolar ventilation. In the absence of these equipment issues, hypercapnia is considered to be a result of inadequate V_A. Because minute ventilation is equal to the product of the respiratory rate and tidal volume, one or both of these ventilator settings can be increased and the PCO_2 concentration reevaluated to determine if the new ventilator protocol is adequate. Alternatively, if the PCO_2 is low, V_A should be decreased.

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213.8.2 Oxygen

The initial arterial blood gas result is evaluated while the patient is breathing 100% oxygen. The first priority is to reduce the FiO_2 to less than or equal to 60% as soon as possible to reduce the risk of oxygen toxicity. The degree to which the FiO_2 can be reduced will be dictated by the measured PaO_2. After any reduction in oxygen concentration, the PaO_2 should be reevaluated. If this is not feasible, constant pulse oximetry monitoring is essential to ensure that the animal does not develop hypoxemia.

Once the FiO_2 can be reduced to less than 60%, the focus then becomes reducing the aggressiveness of the ventilator settings, namely PEEP and the peak inspired airway pressure, in an attempt to minimize the likelihood of ventilator-induced lung injury (see Chapter 26, Ventilator-Associated Lung Injury). In patients with significant pulmonary disease, the PaO_2 obtained with the initial ventilator settings may not allow sufficient reductions in FiO_2.

In severe cases hypoxemia will persist despite ventilation with 100% oxygen. In these animals an increase in the aggressiveness of the ventilator settings is required. Increases in PEEP, peak inspired airway pressure, or respiratory rate may help improve the oxygenating efficiency of the lung.[1] The following chapter on advanced mechanical ventilation will discuss aggressive ventilator protocols in more detail. Prone positioning will maximize lung function in most patients, and animals with hypoxemia should be maintained in sternal recumbency until stabilized.

213.9 MAINTENANCE OF MECHANICAL VENTILATION

Short-term mechanical ventilation (less than 24 hours) requires appropriate monitoring and nursing care but is feasible in most practice situations. Long-term mechanical ventilation is far more challenging and requires a well-staffed, 24-hour facility. Patient care issues such as cardiovascular support, nutritional support, airway care, and prevention of decubitus ulcers require continuous evaluation and treatment in order to prevent significant, life-threatening complications (see Chapter 216, Care of the Ventilator Patient).

213.10 COMPLICATIONS

Mechanical ventilation is not benign; cardiovascular compromise, ventilator-induced lung injury, ventilator-associated pneumonia, and pneumothorax are all common issues for ventilator patients.[1,2,6] Cardiovascular compromise by impairment of intrathoracic blood flow is often an issue for patients with cardiovascular instability or when aggressive ventilator settings are necessary. Cardiovascular monitoring is recommended for all ventilator patients and is essential when high PEEP levels or more aggressive ventilator settings are used. Volutrauma and repetitive alveolar collapse are believed to be the major causes of ventilator-induced lung injury and may be reduced with protective ventilation strategies (see Chapter 214, Advanced Mechanical Ventilation).[7] Aseptic airway procedures, intensive oral care, and reducing the incidence of gastric regurgitation are all important in preventing ventilator-associated pneumonia.[1,2] Patients should be monitored continuously for evidence of infection and changes in pulmonary function. Early signs of pneumonia are an indication for antibiotic administration; culture and sensitivity from an endotracheal lavage or bronchoalveolar lavage sample is always desirable.

Pneumothorax is a well-reported complication of mechanical ventilation, especially when high airway pressures and large tidal volumes are used.[1,2] Minimizing the aggressiveness of ventilator settings should be the constant goal of ventilator management. Pneumothorax should be a primary consideration when a patient has an acute decline in oxygenating ability, elevation in PCO_2, decreased chest wall movement and compliance, and patient-ventilator asynchrony. If not diagnosed and treated rapidly, a tension pneumothorax can prove rapidly fatal in animals receiving positive-pressure ventilation. Unilateral or bilateral thoracostomy tubes with continuous drainage are indicated when managing these ventilated animals.

213.11 TROUBLESHOOTING

Patient-ventilator asynchrony, called *bucking the ventilator,* is a common issue and should be considered a sign of patient distress. Evaluation of the causes of distress should begin with the most life-threatening problems. Issues for consideration include airway patency, oxygenation and ventilation status, body temperature, anesthetic depth, patient comfort, and the suitability of the ventilation protocol.

If a sudden decrease in oxygenation occurs, the oxygen supply to the machine should be checked as well as confirmation that the breathing circuit is intact and the ventilator is delivering breaths as desired. The patient should then be examined to rule out a pneumothorax. In the absence of mechanical failure or a pneumothorax, deterioration in oxygenation is a sign of progression of pulmonary disease or the acquisition of a new pulmonary disease process. If the patient has become hypoxemic, the FiO_2 should be increased immediately to 100% and the animal placed in sternal recumbency until the condition is improved.

Sudden elevations in PCO_2 can occur as a consequence of increased apparatus dead space, occlusion of the breathing circuit or endotracheal tube, pneumothorax, patient-ventilator asynchrony, and reductions in effective alveolar ventilation. If no mechanical abnormalities are evident and pneumothorax is ruled out, then the ventilator settings can be changed to increase minute ventilation. Hypercapnia may be an acceptable consequence of some protective ventilation strategies.[1,2,5,7]

213.12 PROGNOSIS

Prognosis for successful weaning from mechanical ventilation is largely dependent on the primary disease process. Human and veterinary clinical studies have repeatedly reported lower weaning rates for patients requiring ventilation for pulmonary parenchymal disease (inability to oxygenate) compared with patients with neuromuscular disease processes (inability to ventilate). From the few veterinary studies available it appears that approximately 30% of patients ventilated for pulmonary parenchymal disease are successfully weaned compared with 50% or more of patients with neuromuscular disease processes (see Chapter 217, Discontinuing Mechanical Ventilation). 903

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213.13 SUGGESTED FURTHER READING*

SC Haskins, LG King: Positive pressure ventilation. In LG King (Ed.): *Textbook of respiratory disease in dogs and cats*. 2004, Saunders, St Louis, *A detailed discussion of mechanical ventilation in veterinary patients in the context of an excellent reference textbook on respiratory disease.*

NR MacIntyer, RD Branson: In *Mechanical ventilation*. 2001, Saunders, Philadelphia, *One of the few textbooks available that is dedicated to mechanical ventilation and provides a comprehensive review of the relevant topics. A human medical textbook, so some of the information is not relevant to veterinary patients.*

MJ Tobin: Mechanical ventilation. *New Engl J Med*. **330**, 1994, 1056, *An excellent review of mechanical ventilation. Easy to read and a good supplement to other resources but lacks depth and addresses only some of the major issues.*

JB West: In *Respiratory physiology: the essentials*. ed 7, 2005, Lippincott Williams & Wilkins, Baltimore, *A simple, short, easy-to-understand presentation of respiratory physiology. An essential “first” book for anyone interested in this area.*

* See the CD-ROM for a complete list of references

214 Chapter 214 Advanced Mechanical Ventilation

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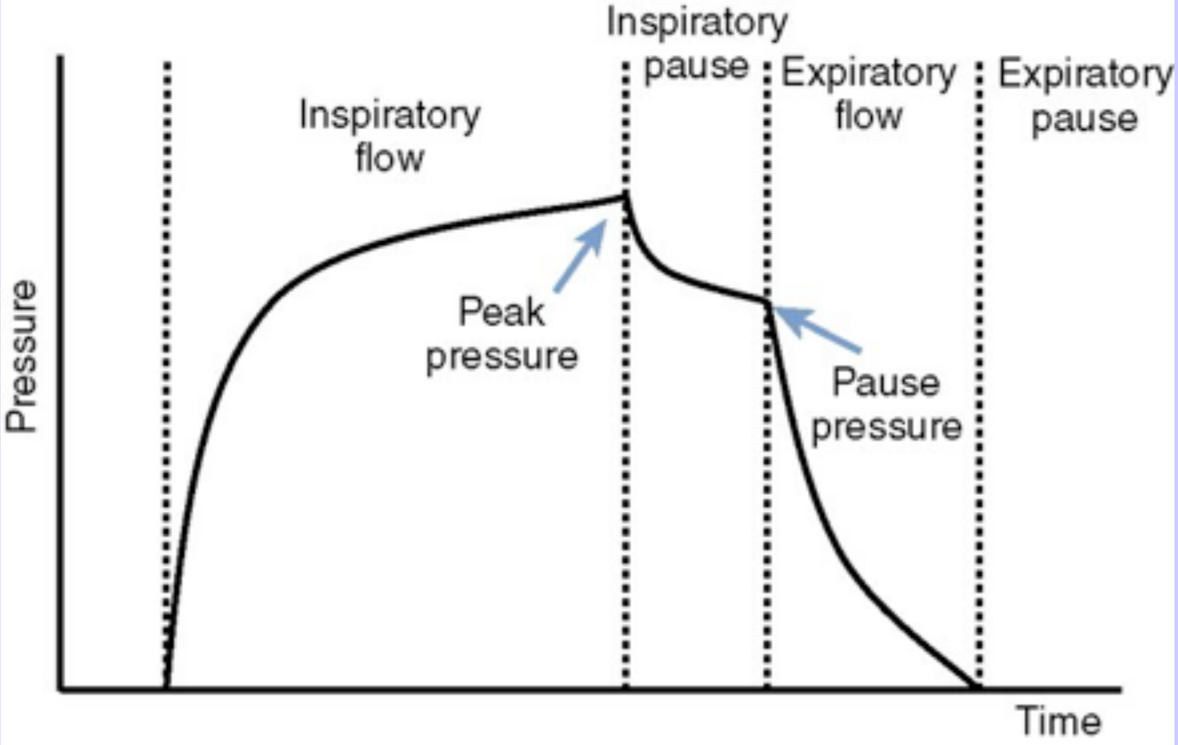
Figure 214-1 The respiratory cycle.



214.1 KEY POINTS

- The ventilator mode is defined by the control variable, breath pattern, and phase variables selected.
- Ventilator breaths can be volume controlled or pressure controlled. The three main breath patterns are continuous mandatory ventilation, continuous spontaneous ventilation, and intermittent mandatory ventilation.
- The goal of selection of the ventilator mode is to provide adequate gas exchange while preventing ventilator-induced lung injury.
- Lung-protective strategies may be important for management of severe, diffuse lung disease such as acute respiratory distress syndrome.
- Patient-ventilator asynchrony is a common, often unrecognized problem that can impair effective gas exchange, increase work of breathing, and create patient discomfort.

- Ventilator waveforms and loops can provide valuable information about ventilator function, patient physiology, and the patient-ventilator interaction.

214.2 VENTILATOR CONCEPTS

An understanding of ventilator function requires an appreciation of how the machine is generating and controlling a given breath. This requires knowledge of what is determining each phase of the breath and where the energy for that breath is derived (i.e., patient or ventilator).

214.2.1 Respiratory Cycle

The respiratory cycle can be divided into four phases: (1) the inspiratory flow phase, (2) the inspiratory pause phase, (3) the expiratory flow phase, and (4) the expiratory pause phase (Figure 214-1).[1,2] By defining how each respiratory phase is determined, the ventilator mode can be described. The respiratory phases also provide a context in which to define common ventilator parameters. For example, peak airway pressure is the maximal airway pressure measured during the inspiratory flow phase. The plateau pressure is the airway pressure measured at the end of the inspiratory pause. The difference between the peak inspiratory pressure and plateau pressure is usually minimal in patients with normal lungs. Some pulmonary disease processes that increase airway resistance (e.g., asthma) can cause significant differences between the peak and plateau pressures.

214.2.2 Equation of Motion

Patient-ventilator interactions can be described by the equation of motion. This equation is built into the ventilator software and is the basis for machine operation (Box 214-1).[2-4] The equation of motion states that the pressure required to deliver a breath depends on the tidal volume and flow of the breath in addition to the resistance and compliance of the system. The resistance and compliance are determined largely by the characteristics of the patient while pressure, volume, and flow are the three interdependent variables that may be manipulated by the machine. To understand a ventilator breath, knowledge of changes in airway pressure, volume, and flow during each respiratory phase is required.

214.2.2.1 Box 214-1 Equation of Motion

Pressure = (tidal volume ÷ compliance) + resistance × flow

214.3 DEFINING THE VENTILATOR MODE

The ventilator mode is defined by nature of the breath type and pattern, control variable, and phase variables used.

214.3.1 Breath Types

A ventilator breath is one of two major types: mandatory or spontaneous. During a spontaneous breath, the patient is responsible for both initiation and termination of inspiration. If the machine controls one or both of these factors, the breath is considered mandatory. When a mandatory breath is initiated by the patient, it is classified as an assisted breath. A spontaneous breath in which inspiration is augmented above baseline by the machine is considered a supported breath (Table 214-1).[2-4]

214.3.2 Control Variable

The control variable is the primary variable manipulated by the machine to generate an inspiration.[2-4] Because flow and volume are interrelated, ventilator breaths are either volume controlled or pressure controlled. In a pressure-controlled breath the machine will maintain airway pressure at a constant, preset (by the operator) level, and inspiration ends when a preset inspiratory time is reached. The tidal volume and gas flow rate generated during this breath are dependent on the magnitude of the preset airway pressure and the resistance and compliance inherent to that system as per the equation of motion.

During a volume-controlled breath the flow and tidal volume are fixed to a level preset by the operator; the machine will maintain a constant gas flow, and the inspiration ends when a preset tidal volume is delivered. As the equation of motion describes, airway pressure reached during these breaths is dependent on the magnitude of the preset tidal volume and the resistance and compliance of the patient's respiratory system.[2-4] The basic waveforms for a pressure-controlled and a volume-controlled breath are shown in Figure 214-2. Exhalation is passive, and it can be seen that it has an exponential character.

214.3.3 Phase Variables

The respiratory cycle helps define the four phases of a breath that can be controlled by the ventilator (see Figure 214-1): (1) the start of inspiration, (2) inspiration, (3) the end of inspiration, and (4) exhalation.[2,3]

214.3.3.1 Cycle Variable

This is the parameter by which inspiration is terminated.[2-4] For example, to give a pressure-controlled breath, the ventilator maintains gas flow at a preset pressure for a given time. When that time has elapsed, inspiration is terminated and exhalation begins, so time is the cycle variable. Time is the most common cycle variable and will be determined by the preset respiratory rate and the inspiratory-to-expiratory (I:E) ratio. An inspiratory time of approximately 1 second is a common guideline.

214.3.3.2 Trigger Variable

This is the parameter that initiates inspiration. It is how the ventilator determines when to deliver a breath.[2-4] In animals that are not making respiratory efforts of their own, the trigger variable will be time and is determined from the set respiratory rate. If the animal is making respiratory efforts, the trigger variable may be a change in airway pressure or gas flow in the circuit resulting from the patient attempting to initiate inspiration. The trigger sensitivity of the machine usually can be set by the operator. An airway pressure drop of 2 cm H_2O or gas flow change of 2 L/min are usually effective trigger sensitivities. Appropriate trigger sensitivity is essential to ensure that ventilator breaths are synchronized with genuine respiratory efforts made by the patient. This increases comfort and allows the patient to increase its respiratory rate as required. The trigger variable can be too sensitive, such that nonrespiratory movements such as patient handling may initiate breaths, and this should be prevented.

214.3.3.3 Limit Variable

This is a parameter that the breath cannot exceed during inspiration, but it is different from the cycle variable because it does not terminate the breath.[2-4] This variable may be found on modern intensive care ventilators. For example, a volume-controlled, pressure-limited breath means that the ventilator will generate the breath by delivering a preset tidal volume, but it will not exceed the limit set for airway pressure at any time during the delivery.

214.3.3.4 Baseline Variable

This variable is controlled during exhalation; airway pressure is the most common baseline variable manipulated.[2-4] If airway pressure during exhalation is maintained above atmospheric pressure, this is referred to as *positive end-expiratory pressure (PEEP)*.

214.3.4 Breath Patterns

214.3.4.1 Continuous Mandatory Ventilation

In this mode of ventilation a minimum respiratory rate is set by the operator. If the trigger sensitivity is set appropriately, the patient can increase the respiratory rate but all breaths delivered will be of a mandatory type. If the patient is unable to trigger breaths, it is considered controlled ventilation. More commonly patients are allowed to trigger their own respiratory rate and this is called assist-control ventilation. The terms *controlled mechanical* and *assist-control ventilation* generally are used interchangeably.[2-4]

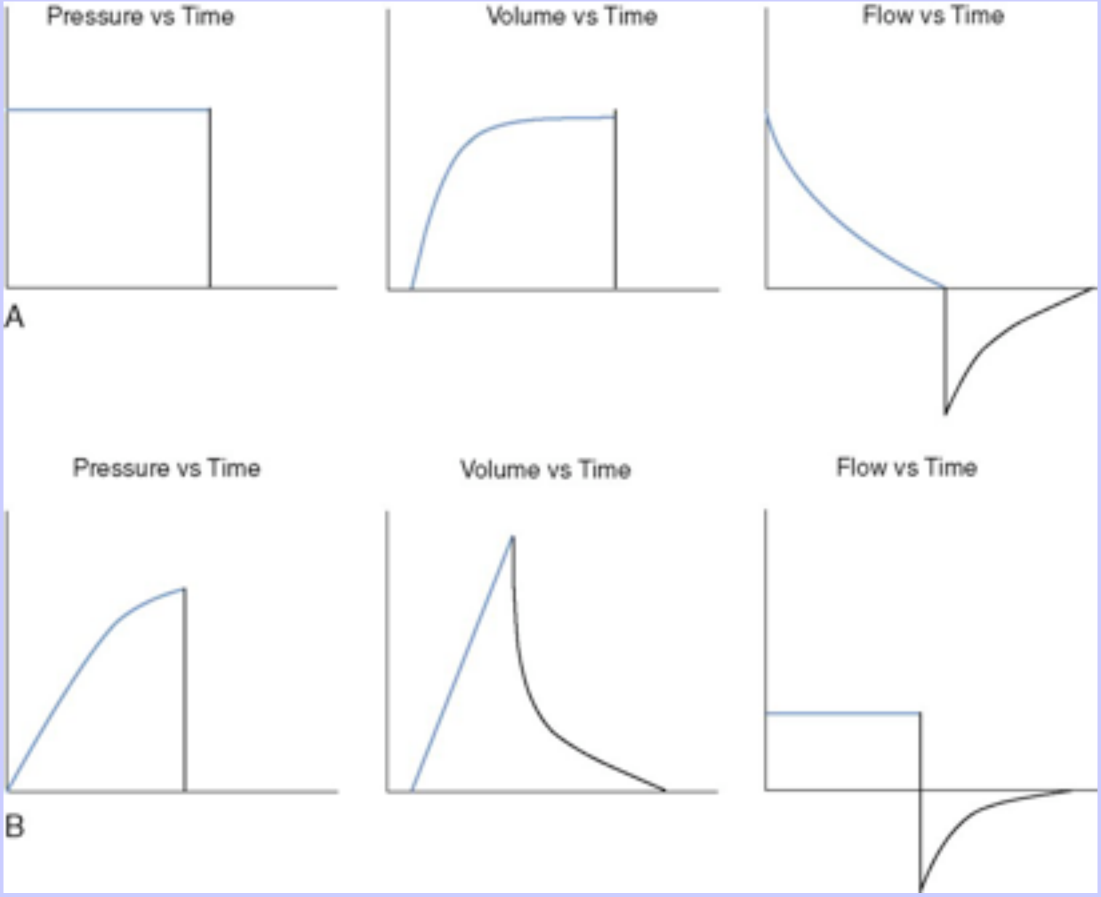
214.3.4.2 Intermittent Mandatory Ventilation

In this mode a set number of mandatory breaths is delivered with either pressure or volume control. Between these breaths patients can breathe spontaneously as often or as little as they choose. In modern ventilators the machine tries to synchronize the mandatory breaths with the patient's inspiratory efforts, a pattern called *synchronized intermittent mandatory ventilation.* 905 906 If no breaths are detected by the machine during the period of synchronization, a mandatory breath will be given. The operator can control only the minimum respiratory rate and minimum minute ventilation; there is no control over the maximum rate or maximum minute ventilation.[2-4]

Table 214-1 Comparison of the Four Clinically Different Ventilator Breath Types

Breath Type	Initiation (Trigger)	Termination (Cycle)	Inspiratory Flow
Mandatory	Ventilator	Ventilator	Ventilator
Assisted	Patient	Ventilator	Ventilator
Spontaneous	Patient	Patient	Patient
Supported	Patient	Patient	Ventilator

Figure 214-2 Pressure, volume, and flow as related to time waveforms for pressure-controlled and volume-controlled ventilation. (Note the inspiratory portion of each waveform is in blue.) **A,** In pressure-controlled ventilation, airway pressure is maintained at a constant level throughout the inspiration, volume increases with time, and the flow rate of the breath decelerates as the lungs fill with gas. **B,** In volume-controlled ventilation, the flow rate is held constant throughout inspiration, but tidal volume and airway pressure both increase with time.



214.3.4.3 Continuous Spontaneous Ventilation

Every breath of continuous spontaneous ventilation is triggered and cycled by the patient; consequently this breath pattern can be used only in patients with a reliable respiratory rate. The inspiratory time and tidal volume are also determined by the patient. The two most common forms of this mode are continuous positive airway pressure (CPAP) and pressure support ventilation (PSV).

CPAP provides a constant level of positive pressure (preset by the operator) throughout the respiratory cycle. CPAP increases functional residual capacity and compliance, enhancing gas exchange and oxygenation; it does not augment airflow during inspiration. CPAP is used most commonly for spontaneous breathing trials in an attempt to evaluate if a patient can be disconnected from the ventilator.[2-4]

In PSV the ventilator provides a constant preset level of airway pressure during inspiration. This reduces the effort required to maintain spontaneous breathing in patients with adequate respiratory drive but inadequate ventilatory strength. The degree of support provided will depend on the magnitude of pressure support given. PSV can help overcome the resistance of breathing through the endotracheal tube and ventilator breathing circuit.[2-4] It can be used alone, in conjunction with PEEP, or to augment the spontaneous breaths during synchronized intermittent mandatory ventilation or CPAP. PSV is used most commonly as a step-down mode from CMV or synchronized intermittent mandatory ventilation during the weaning process. The cycle variable in PSV is flow; the ventilator ceases providing inspiratory pressure when it senses a decrease of 20% to 25% (depending on the machine) in flow rate, signaling exhalation.

214.3.5 Ventilator Mode

The basic definition of a ventilator mode requires identification of the control variable and the breath pattern: 906 pressure-controlled or continuous mandatory ventilation. A more detailed definition would include a description 907 of the nature of any phase variables being used; these include pressure-controlled, continuous, mandatory, pressure-triggered, and time-cycled ventilation with PEEP.

214.4 RESPIRATORY RATE AND INSPIRATORY-TO-EXPIRATORY RATIO

The mandatory respiratory rate can be set on all ventilators. A normal respiratory rate of 15 to 20 breaths is usually selected when assisted ventilation is initiated. This can then be changed as appropriate. The I:E ratio may be preset by the operator, or in some older ventilators it is a default setting within the machine. Depending on the ventilator, the I:E ratio may be set directly or indirectly by manipulation of inspiratory time, percent inspiratory time, or inspiratory flow rate in conjunction with the respiratory rate. An I:E ratio of 1:2 with inspiratory times of approximately 1 second are used to ensure that the patient has exhaled fully before the onset of the next breath. As respiratory rates are increased, the expiratory time will be sacrificed to “squeeze” in the necessary number of inspirations.

High respiratory rates can lead to a situation known as breath stacking or intrinsic PEEP, because the animal is not able to exhale fully before the start of the next inspiration. Longer inspiratory times can be used in an effort to improve oxygenation. In some lung disease processes, a reverse I:E ratio (where inspiration is longer than exhalation) has been found beneficial, but this should be used with caution because associated intrinsic PEEP and hemodynamic compromise can have serious consequences.[2-4]

214.5 POSITIVE END-EXPIRATORY PRESSURE

PEEP is achieved by maintaining a pressure above atmospheric pressure during the expiratory phase of the breath. Extrinsic PEEP is a baseline phase variable that can be set on most modern ventilators. In addition, intrinsic PEEP can be developed as a consequence of inadequate time for exhalation. Physiologically intrinsic PEEP has effects on pulmonary function and hemodynamics identical to those of extrinsic PEEP.[2-4]

Pulmonary parenchymal disease creates areas of low ventilation to perfusion (low V/Q) and areas of alveolar collapse (no V/Q), leading to decreased oxygenating or ventilating ability, or both. When pulmonary disease causes severe hypoxemia that will not resolve with oxygen therapy alone, positive-pressure ventilation is indicated (see Chapter 213, Basic Mechanical Ventilation). In patients with acute lung injury, PEEP can open or “recruit” previously collapsed alveoli and prevent further collapse of unstable alveoli, improving V/Q matching and hence improving oxygenation. Appropriate levels of PEEP can improve pulmonary compliance and reduce the work of breathing, although excessive PEEP can decrease compliance. Appropriate use of PEEP is also thought to reduce ventilator-associated lung injury by preventing shear injury associated with the cyclic reopening and collapse of alveoli with each breath (see Chapter 26, Ventilator-Associated Lung Injury).[5,6]

PEEP can also have detrimental effects; it can cause overdistention of healthier alveoli, which have a higher compliance. PEEP may also reduce cardiac output by impairing venous return during the expiratory phase. This effect is greatest when pulmonary compliance is high and preexisting cardiovascular compromise is present, such as in patients with hypovolemia. Hemodynamic monitoring is recommended for all ventilated patients and is essential when high levels of PEEP or more aggressive ventilator settings are used.[2-5]

214.6 LUNG-PROTECTIVE VENTILATION

It is now recognized that positive-pressure ventilation triggers an inflammatory response in the lungs, and the degree of this response is determined by the ventilation strategy employed. It has been well demonstrated that overdistention of alveoli is injurious and should always be prevented.[6] In many patients this can be achieved by maintaining recommended tidal volumes when designing a ventilation protocol. In patients with severe lung disease such as acute respiratory distress syndrome (ARDS), the normal recommended tidal volumes may be excessive. ARDS causes collapse and consolidation of alveoli, leaving fewer aerated lung regions. These regions would be vulnerable to overdistention if a regular tidal volume were delivered.

The ARDS Network reported a significant reduction in mortality of human patients with ARDS who were ventilated with a tidal volume of 6 ml/kg compared with 12 ml/kg. This lung-protective ventilation strategy included high PEEP levels and limited plateau pressures (no higher than 30 cm H_2O).[6] The role of high levels of PEEP in protective lung ventilation remains controversial, and further studies are being performed. A consequence of low tidal volume ventilation is elevations in PCO_2, which can be addressed with interventions such as tracheal gas insufflation. In human patients high PCO_2 levels may be tolerated, a situation referred to as *permissive hypercapnia,* although these patients tend to need heavier sedation or paralysis.[4-6]

The ventilatory strategy of low tidal volumes and moderate to high PEEP, with or without permissive hypercapnia, is considered lung-protective ventilation. Given the evidence from experimental animal studies and human clinical trials, it would be reasonable to assume that lung-protective ventilation has a valid role in veterinary patients. It is important to appreciate that this ventilation strategy is designed for the lung with ARDS and should be applied with caution to those with other disease states.

214.7 PATIENT-VENTILATOR ASYNCHRONY

Patient-ventilator asynchrony occurs whenever there is a mismatch between the machine settings for the trigger sensitivity, gas delivery, or breath cycle determinants and the patient's breathing pattern. Patient-ventilator asynchrony can impair gas exchange, increase the work of breathing, and create a sense of dyspnea for the patient.[2,3,7] Although there are no specific diagnostic criteria for the condition, it is commonly evidenced by animals fighting, or “bucking,” the ventilator.

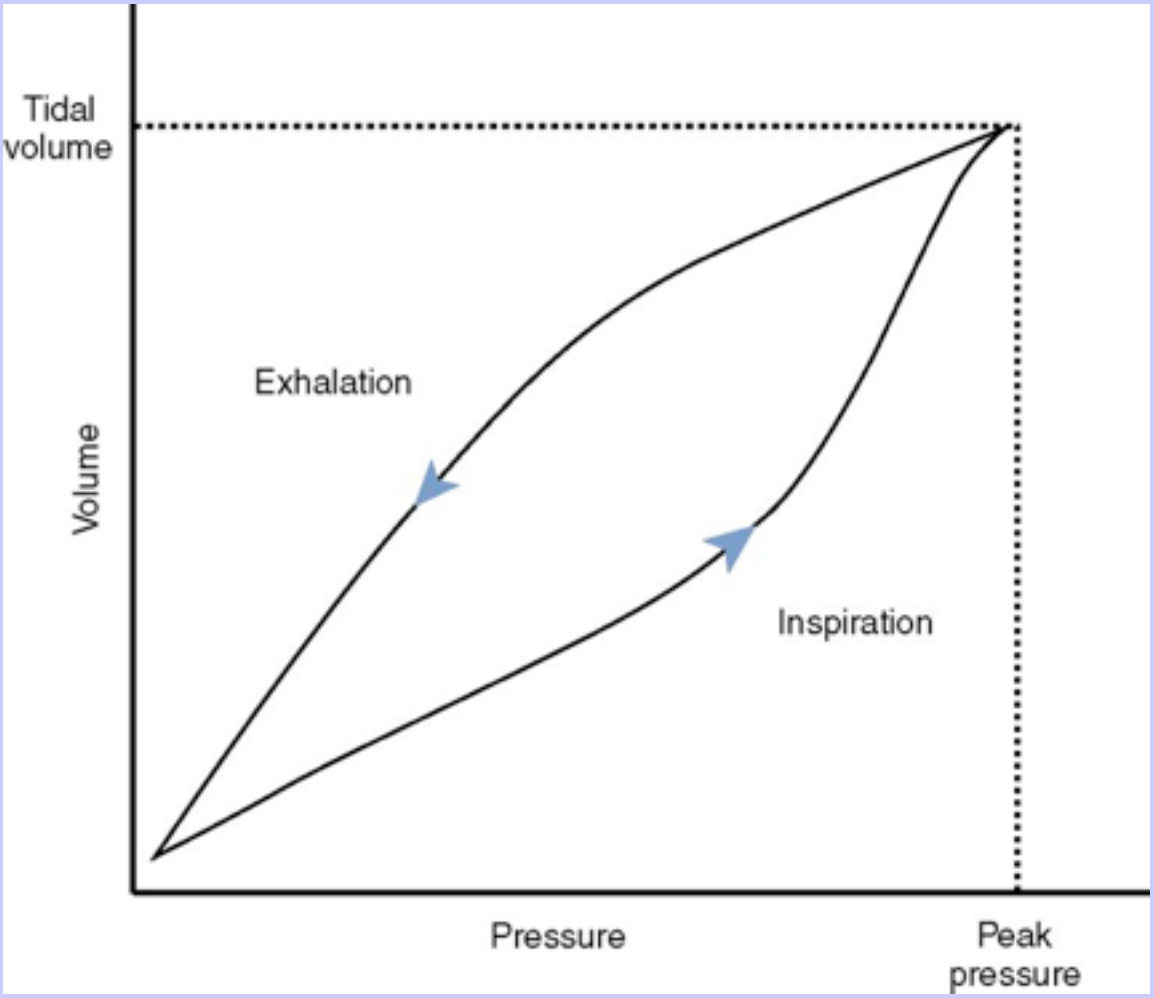
Less obvious signs of patient-ventilator asynchrony may be best observed by studying real-time ventilator waveforms and loops.[2,3,7,8] Studies report that patient-ventilator asynchrony is underestimated and frequently goes unrecognized in human patients, so it is likely that more subtle forms are poorly recognized in veterinary patients as well. In order to try and optimize the patient-ventilator interaction, the operator must continually match the trigger, gas flow, and cycling of breaths to the animal.

Table 214-2 Common Causes of Patient-Ventilator Asynchrony[*]

Nature of Problem	Diagnostic Approach	Therapeutic Approach
Patient Related		
Hypoxemia	Arterial blood gas analysis or pulse oximetry	Increase FiO_2 or magnitude of ventilator settings
Hypercapnia	Arterial or venous blood gas analysis	Check endotracheal tube Increase tidal volume or respiratory rate
Hyperthermia	Temperature monitoring	Provide active cooling
Pneumothorax	Auscultation, blood gas analysis, radiographs, thoracentesis	Thoracentesis Thoracic drain
Drug-induced panting (opioids)	Consideration of respiratory pattern and concurrent drug administration	Consider change in anesthetic or sedation protocol
Inadequate anesthesia depth	Palpebral reflex, jaw tone, heart rate	Increase anesthesia depth
Equipment Related		
Disconnection or circuit leak	Evaluate circuit and endotracheal connection Auscultate neck for cuff leak Observe waveforms	Resolve disconnection or leak
Endotracheal tube kinked, obstructed, dislodged	Observe endotracheal tube position Auscultate chest Evaluate tidal volumes Measure PCO_2	Reposition or replace endotracheal tube
Inappropriate trigger setting	Observe patient's respiratory efforts compared with ventilator responses	Change trigger setting accordingly
Insufficient tidal volume	Animal appears to try to increase inspiratory effort: observe waveforms	Consider increasing tidal volume (caution in patients with ARDS)
Inspiratory time too short	Animal trying to inspire during exhalation: observe waveforms	Increase inspiratory time
Inspiratory time too long	Animal trying to exhale during inspiration: observe waveforms	Decrease inspiratory time

ARDS, Acute respiratory distress syndrome; *FiO_2*, fraction of inspired oxygen; *PCO_2*, partial pressure of carbon dioxide.

Figure 214-3 An idealized pressure-volume loop. Note that for a positive-pressure breath the loop flows in a counterclockwise direction, with inspiration represented by the lower limb and exhalation represented by the upper limb.



Patient-ventilator asynchrony can have ventilator-related or patient-related causes. Because patient requirements can be changing constantly, continuous clinical assessment and physiologic monitoring is required in conjunction with continuous manipulation of the machine settings or patient care in response to changes observed.[2-4,7] Table 214-2 lists common machine-related and patient-related causes of patient-ventilator asynchrony that should be evaluated when troubleshooting this problem. It is important to avoid the knee-jerk reaction of increasing anesthetic depth, because this may mask a significant underlying problem and increases the risk of anesthetic-related complications. 908 909

*   Note: Patients may develop more than one problem concurrently.

214.8 VENTILATOR WAVEFORMS

Modern ventilators provide real-time graphics of the ventilator breath that can be valuable in assessment of ventilator performance, patient physiology, and the patient-ventilator interaction. The most clinically useful graphics are the flow, pressure, and volume versus time waveforms, as well as flow-volume and pressure-volume loops.[2,8]

Figure 214-2 shows a simplified version of flow, pressure, and volume waveforms. Analysis of these can provide information regarding the mode of ventilation, patient triggering, patient ventilator asynchrony, presence of intrinsic PEEP, and airway leaks. When evaluating waveforms, it is always important to identify the ventilator mode, because this will determine what “normal” should be for a given waveform.

Figure 214-3 is a pressure-volume loop. The slope of the pressure-volume curve at a given point reflects the compliance of the chest wall and lung at that lung volume. The shape and orientation of the pressure-volume curve will change with the presence of lung disease and alterations in ventilator settings. The pressure-volume curve can also provide information regarding patient-ventilator asynchrony and airway leaks. A full description of ventilator waveforms and their interpretation is beyond the scope of this chapter and is provided elsewhere.[2,3,8]

214.9 SUGGESTED FURTHER READING*

ARDS Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. **342**, 2000, 1301, *The original study documenting the benefits of low tidal volumes in human patients with ARDS. Ventilation with a 6-ml/kg tidal volume compared with a 12-ml/kg tidal volume associated with a reduced mortality and fewer days on the ventilator*.

DR Hess, RM Kacmarek: In *Essentials of mechanical ventilation*. ed 2, 2002, McGraw-Hill, New York, *An excellent general text on mechanical ventilation that contains all the important information in an easy-to-read fashion*.

SP Pilbeam, JM Cairo: In *Mechanical ventilation: Physiological and clinical applications*. ed 4, 2006, Mosby, St Louis, *A great in-depth resource for mechanical ventilation that has a lot of diagrams and human clinical examples. Ideal for true mechanical ventilation enthusiasts*.

V Squadrone, C Gregoretti, VM Ranieri: Patient-ventilator interaction. In MP Fink, E Abraham, JL Vincent, PM Kochanek (Eds.): *Textbook of critical care*. 2005, Saunders, Philadelphia, *One of several excellent chapters on mechanical ventilation in this textbook. Provides an overview of the major issues contributing to human patient-ventilator asynchrony*.

* See the CD-ROM for a complete list of references

215 Chapter 215 Jet Ventilation

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215.1 KEY POINTS

- Transtracheal jet ventilation can be used for emergency ventilation; high-frequency jet ventilation can be used to ventilate patients when tracheal intubation is not possible or practical.
- High-frequency ventilation can produce normoxemia and normocapnia with tidal volumes less than the volume of the dead space.
- High-frequency ventilation requires very high minute volumes.
- During jet ventilation, distribution of ventilation and tidal volume depend more on airway resistance than on respiratory system compliance.
- Tidal volume and end-tidal carbon dioxide concentration cannot be measured accurately during jet ventilation.
- Adequacy of ventilation and oxygenation should be assessed using blood gas analysis, particularly if jet ventilation is used for extended periods.
- Interpretation of blood gas data should not be influenced by the mode of ventilation (spontaneous versus conventional mechanical versus jet).

215.2 INTRODUCTION

High-frequency ventilation was first explored in the 1960s, in an attempt to find a technique of positive-pressure ventilation that would have minimal impact on circulation.[1] It was assumed that insufflation of gas at a high frequency, directly into the airway, would enable a reduction in tidal volume and thereby in intrathoracic pressure.

Various strategies can be used to deliver high-frequency ventilation. These include high-frequency oscillation, high-frequency jet ventilation (or jet ventilation), high-frequency flow interruption, and high-frequency positive-pressure ventilation.[2] This chapter will focus on jet ventilation.

Jet ventilation was first used during bronchoscopy.[1] A cannula was placed in an open-ended bronchoscope, and gas was delivered from a high-pressure source. Ambient air was entrained by the Venturi effect. The system was later adapted to deliver gas through a ventilating laryngoscope, and through a catheter placed between the vocal cords. Percutaneous transtracheal jet ventilation was introduced in anesthesia in the early 1970s.

During jet ventilation, pulses of gas are delivered at high velocity through an orifice in a T-piece connected to a tracheal tube, through a narrow tube incorporated in the tracheal tube, or through a catheter placed in the upper airway.[3] Typical frequencies are in the 100 to 300 breaths/min range.[4] The major advantage of jet ventilation resides in the flexibility of the patient interface, allowing ventilation in situations where tracheal intubation is not possible.

In addition to high-frequency jet ventilation, transtracheal jet ventilation can be used for emergency ventilation, if a tracheal tube cannot be placed. Acceptable gas exchange can be achieved using a high-pressure oxygen source, a valve, a jet injector, a catheter, and noncompliant tubing. A jet injector can be made of a cut-off 1-ml syringe; the flush valve of an anesthesia machine can be used as a valve.[5] Ventilation is then provided at a rate of 12 to 20 breaths/min.[6]

215.3 PHYSICS AND PHYSIOLOGY

High-frequency ventilation is based on the premise that transpulmonary pressure (i.e., the pressure that distends alveoli) can be divided in a steady and an oscillatory component. Eucapnia can then be maintained at low tidal volumes by an increase in the frequency of oscillation.[7] By decreasing tidal excursion (i.e., transpulmonary pressure excursion above and below its mean), high-frequency ventilation should also limit alveolar derecruitment due to insufficient lung volume. Interestingly, panting in dogs may be considered to represent the physiologic counterpart to mechanical high-frequency, low–tidal volume ventilation, and has been used as a model to study gas exchange during conditions of high-frequency ventilation.[8]

The volume of gas delivered to the alveoli depends on the volume of gas passing through the jet, the volume of gas entrained into the tracheal tube or airway, and the volume of the dead space.[9] As frequency increases, tidal volume decreases, but dead-space ventilation increases and alveolar ventilation can therefore be maintained only with very high minute ventilation. At frequencies above 1 Hz (60 breaths/min), tidal volume is usually less than the volume of the dead space. It has been suggested that when tidal volume is less than 1.2 times the volume of the dead space, carbon dioxide (CO_2) elimination is greatly reduced compared with conventional convective gas exchange, and that the length of the dead space has a larger influence than its volume on CO_2 elimination.[9] It may therefore be beneficial to administer jet ventilation as distally as possible or practical.

However, it has been shown that the physical characteristics of a jet depend on the ratio of the jet diameter to tube or airway diameter, the ratio of jet diameter to tube length, the position of the jet entrance, and the driving pressure.[10] Injectors can be designed to maximize flow. With distal jet ventilation, optimization of the injector is not possible, potentially resulting in decreased efficiency and flow.

Although the gas volume of the jet after a single injection may not travel more than a few diameters, a continuing distal motion of previously injected gas occurs with the repetition of this jet injection, particularly at high frequencies.[11] High-frequency jet ventilation results in inhomogeneous ventilation.[12] Regional variation in gas 910
concentration, air space volumes, and pressures are observed. Caudal lung lobes usually are ventilated better, due to 911
inertial factors. However, this lack of uniform ventilation is expected to have minimal impact on overall gas exchange.

The volume of the jet impulse (tidal volume) is influenced by the geometry of the injector, the amount of gas entrained, the pressure of the jet, the back pressure, and the impulse duration.[10] Effective injectors can entrain 4 to 5 times the jet flow during the early part of inspiration,[4,10] although some studies suggest that this effect is minimal.[13] The entrained volume, measured as a fraction of the tidal volume, is minimally affected by respiratory rate in the 12 to 200 breaths/min range.[14] Entrainment is optimized by positioning the jet entrance in the proximal part of the endotracheal tube.[10] Entrainment is due to a Venturi effect as a high velocity gas stream exits the injector.[14] Entrainment is limited to the early part of inspiration (first 0.08 second, regardless of respiratory rate), because as the lungs begin to fill the airway pressure increases, which opposes, and eventually prevents, entrainment of gas.

For the remainder of inspiration, some of the jet gas comes out of the airway opening without entering the lungs.[14] The amount of gas lost this way (spilled volume) decreases as respiratory rate increases. During gas entrainment, there can be no spillage. As respiratory rate increases, inspiratory time decreases, but the time during which entrainment occurs remains fairly constant; therefore the time available for spillage decreases.[14] Because high frequencies are required, expiratory time is short, and end-expiratory lung volume is increased. Therefore end-expiratory pressure is usually positive. This raises the pressure at the beginning of inspiration and may limit gas entrainment when high respiratory rates are used. Because of the high velocity of gas flow required to produce adequate ventilation at these high frequencies, changes in airway resistance will have a larger effect on tidal volume than respiratory system compliance, especially because volume changes are minimal. Similarly, distribution of ventilation will depend more on airway resistance than regional compliance, which may be beneficial in lung diseases that do not affect the airway.[7]

215.4 EQUIPMENT

Various devices to administer jet ventilation are commercially available. They are based on a high-pressure gas source and solenoid valves to admit and/or interrupt gas flow. Typical settings include peak airway pressure, respiratory rate, and inspiratory time, or inspiratory-to-expiratory time ratio. Some ventilators allow the control of mean airway pressure, positive end-expiratory pressure, minute volume, and/or driving pressure. Rates usually range from 30 to 150, sometimes as high as 600 breaths/min.

215.5 INDICATIONS

Jet ventilation is indicated when mechanical ventilation is necessary or beneficial but traditional positive-pressure ventilation cannot be delivered. This may include laryngeal and tracheal surgery, bronchial resection, laryngoscopy, and bronchoscopy, and whenever limitation of movement associated with respiration is beneficial.[15] In addition, it has been suggested that jet ventilation in acute respiratory failure with circulatory shock resulted in higher cardiac output than traditional ventilation.[16] It is indicated if ventilation is required in patients with a tracheal lesion secondary to tracheostomy or prolonged intubation.[15] Jet ventilation may also be used if the laryngeal opening is too small to allow intubation. It has been suggested that, because of lower peak airway pressure than in traditional mechanical ventilation, jet ventilation may be preferable in airway leak situations.[17]

In dogs and cats, high-frequency jet ventilation has been used to maintain oxygenation and ventilation during resection and anastomosis of the intrathoracic trachea and during bronchoscopy.[18,19]

We mainly use jet ventilation to maintain oxygenation and CO_2 elimination during bronchoscopy in dogs of small size and in cats. We deliver ventilation through a 14- or 16-gauge catheter positioned in the trachea (Color Plate 215-1). The bronchoscope can then be passed alongside that catheter (Color Plate 215-1).

Transtracheal high-frequency jet ventilation can be used in emergency situations. A catheter is placed percutaneously through the cricothyroid membrane. The catheter is then secured to the patient's neck. Migration of the catheter outside of the trachea would result in severe subcutaneous emphysema.[17]

215.6 DISADVANTAGES

Tidal volume is very difficult to measure during jet ventilation. The high velocity of the jet and entrainment of additional gas make inspiratory volume measurement very difficult; spillage of gas out of the open airway and the common addition of a bias flow make measurement of expired volume inaccurate.[14] Similarly, end-tidal carbon dioxide concentration cannot reliably be measured.[3] Therefore adequacy of ventilation should be confirmed by end-tidal carbon dioxide concentration measurement during intermittent ventilation with large tidal volume, or by arterial blood gas analysis.

Jet ventilation may cause fluctuations in the amplitude of chest excursions, and phasic changes in heart rate and systemic and pulmonary arterial pressures, resulting in fluctuations in blood flow.[20] The small tidal volumes and therefore low peak airway pressure and possibly mean airway pressure during jet ventilation are expected to limit the cardiovascular effects of this mode of ventilation. However, compared with conventional mechanical ventilation, high-frequency jet ventilation may result in similar, larger, or smaller cardiovascular effects.

Jet ventilation, particularly during severe bronchoconstriction or other forms of airway obstruction, may result in lung overinflation, as gas accumulates because of short expiratory times. Lung hyperinflation may also result from steady alveolar pressure in excess of steady airway pressure.[7] This is likely due to unequal inspiratory and expiratory impedances, distribution of oscillatory flow, and expiratory flow limitation.[11,21] In addition, high-velocity gas streams as generated during high-frequency ventilation preferentially follow straight pathways. Because of the geometry of the central airway, this may result in regional differences, with an increased tendency of the lung base to be overinflated compared with the apex.[7]

Prolonged use (i.e., hours) of high-frequency jet ventilation administered in the trachea via a catheter was shown to result in endoscopic evidence of tracheal injury characterized by hypervascularity, mucus accumulation, focal hemorrhage, linear epithelial loss, and/or diffuse erythema and epithelial loss.[22]

215.7 MONITORING OF GAS EXCHANGE DURING JET VENTILATION

Despite the technical difficulties limiting the ability to monitor the adequacy of ventilation during high-frequency jet ventilation, the same principles as for conventional mechanical ventilation apply.[23] Arterial blood gas analysis remains the gold standard to judge adequacy of oxygenation and ventilation, and should be available if jet ventilation is used for extended periods. The same normal and abnormal PaO_2 and $PaCO_2$ values as during conventional mechanical ventilation should be used when interpreting blood gas data. Similarly, intrapulmonary gas exchange efficiency can be assessed using the alveolar-arterial PO_2 difference or (with more limitations) the PaO_2-to-FiO_2 ratio.

215.8 VENTILATOR SETTINGS

The goal of jet ventilation is to maintain adequate oxygenation and CO_2 elimination. However, because of the characteristics of this method it is difficult to give guidelines for adjusting ventilatory parameters that will result in normal ventilation in various situations.[4] Our clinical experience suggests that at a frequency of 180 breaths/min with tidal volumes resulting in barely detectable chest excursions usually results in adequate oxygenation and normocapnia to moderate hypocapnia. One study in dogs and cats reported that with driving pressures of 0.33 kg/

cm^2 and an inspiratory-to-expiratory ratio of 1:2, cats were mildly hyperventilated at a frequency of 140 breaths/min; in dogs, a driving pressure of 1.3 to 1.8 kg/cm^2 and 120 to 150 breaths/min resulted in a similar degree of hyperventilation.[17]

215.9 SUGGESTED FURTHER READING*

D Bohn: The history of high-frequency ventilation. *Respir Care Clin North Am*. **7**, 2001, 535, *Good review article on the development of high-frequency ventilation techniques*.

SC Haskins, H Orima, Y Yamamoto, et al.: Clinical tolerance and bronchoscopic changes associated with transtracheal high-frequency jet ventilation in dogs and cats. *J Vet Emerg Crit Care*. **2**, 1992, 6, *Good research article on the consequences of long-term jet ventilation in dogs and cats*.

* See the CD-ROM for a complete list of references

216 Chapter 216 Care of the Ventilator Patient

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216.1 KEY POINTS

- Ventilator patient care requires specialized equipment, extensive monitoring, and dedicated, trained staff.
- Inadequate care can lead to life-threatening complications for the ventilator patient.
- Oropharyngeal bacterial colonization is a leading cause of ventilator-associated pneumonia and can be minimized by strict adherence to oral care protocols.
- Maintenance of airway hygiene is essential; anything entering the upper airway, such as endotracheal tubes or suction catheters, should be sterile.

216.2 INTRODUCTION

Mechanical ventilation is becoming more common in small animal medicine. These patients are usually anesthetized and are totally dependent on their caregivers. The major complications seen in ventilator patients can be minimized or prevented with appropriate nursing care and dedicated, trained caregivers. The challenges of caring for short-term (1 to 24 hours) and long-term (days to weeks) ventilator patients are different. Short-term ventilator patients may not require such specialized equipment or intensive care, but those being ventilated over a long term may have unique management requirements. Detailed patient records are essential, and a ventilator record sheet is often helpful (Box 216-1).

In one small animal study of long-term ventilation, many of the complications seen were related to nursing care issues, including endotracheal (ET) tube occlusion and accidental disconnections, tracheal necrosis, oral and ocular ulcers, pressure sores, muscle atrophy, and peripheral edema.[1] This chapter reviews basic concepts in ventilator patient care.

216.3 AIRWAY

216.3.1 Intubation

Airway management is an essential aspect of ventilator patient care. For most patients this is accomplished via ET intubation and general anesthesia. It is important that ET tubes are sterile and ideally have high-volume, low-pressure cuffs. Tracheal mucosal blood flow can be occluded by pressures over 25 to 35 mm Hg.[2] Ideally cuff pressure should be maintained between 20 and 25 mm Hg and measured regularly with a pressure gauge. Higher pressures impede mucosal blood flow and may lead to tracheal necrosis. Lower cuff pressures are associated with an increased risk of aspiration.[2-4] In practice, the cuff should be inflated while auscultating the trachea until no leak is heard and then deflated slightly until a small leak can first be detected. Although frequently used, the pilot balloons do not correlate well with cuff pressure and should not be used as an indicator of appropriate inflation.[3]

Tracheal injury can also be minimized by repositioning the ET tube every 4 hours. This is achieved by deflating the cuff, repositioning the tube slightly to change the pressure point, and then reinflating the cuff. The mouth and pharynx should be flushed and suctioned before deflating the cuff.[3]

ET tubes should be tied securely with intravenous tubing or another nonporous material, which is less likely than gauze to become saturated with oral secretions and bacteria. The ties should be moved and secured in a different position every 4 hours to prevent lip necrosis.

The ET tube should be changed every 24 to 48 hours depending on the amount and character of the secretions. It is important to preoxygenate with 100% oxygen before changing the tube and to be prepared for a difficult reintubation.[3] Sterile ET tubes should be used in all ventilator patients.

Patients such as those with neurologic or neuromuscular disease that cannot fight mechanical ventilation often can be managed with a tracheostomy tube and light sedation instead of ET intubation and general anesthesia. This may provide the benefits of allowing ongoing neurologic evaluation, decreased need for anesthesia, and the ability of some patients to eat and drink on their own while being ventilated.[5] It is important to consider that some of these patients may require anxiolytic and/or analgesic drugs to control associated distress or discomfort associated with mechanical ventilation.[3,5]

216.3.1.1

Box 216-1 Sample Ventilator Patient Treatment Sheet

- Evaluate and record ventilator settings q2h
- Monitor depth of anesthesia and adjust infusions q2h
- Suction endotracheal tube and instill saline if needed q4h
- Adjust tube ties and cuff q4h
- Clean tracheostomy tube cannula and site q4h
- Change endotracheal tube q24-48h
- Turn patient, record position, and check padding and heat support q4h
- Do passive range-of-motion exercises q4h
- Lubricate eyes q2h
- Flush and suction mouth and pharynx q4h
- Clean mouth with oral chlorhexidine solution q4h
- Reposition pulse oximetry probe and wrap tongue with saline or glycerine gauzes q2h
- Palpate bladder and measure urine output q4h
- Provide urinary catheter care q8h
- Perform intravenous catheter care q24h

- Change heat and moisture exchanger and ventilator tubing q48-72h
- Monitor continuously and record the following values q2h
    - Electrocardiogram (heart rate and rhythm)
    - Blood pressure (direct, Doppler, or oscillometric)
    - Pulse oximeter
    - End-tidal carbon dioxide
    - Rectal temperature
    - Central venous pressure

Tracheostomy tubes ideally should have an inner cannula that should be cleaned every 4 hours and the entire tracheostomy tube changed every 24 to 48 hours. If there is no cannula, the tube should be suctioned regularly and changed every 24 hours. The tracheostomy tube should also have a cuff to protect the airway from migration of oral secretions and to allow positive end-expiratory pressure (PEEP) to be used.[2,3]

216.3.2

Humidification and Suction

Anesthetized patients are not able to cough or clear airway secretions effectively, and occlusion of the tube lumen is a common and potentially life-threatening problem.[1] Prevention of airway occlusion requires adequate humidification and suctioning.

Gas flow bypasses the nasal passages during mechanical ventilation and is therefore not humidified or filtered by the body. This can lead to a loss of heat and moisture, which can damage the respiratory epithelium. Humidification is also critical in making secretions less viscous and easier to remove.[2,3,6]

Humidifiers can be divided broadly into two groups: high flow and passive. High-flow humidifiers are connected to the ventilator circuit and generally involve a heated element and a sterile water reservoir to add moisture and heat to the gases. These humidifiers are expensive but are very effective. It is important to monitor the respiratory circuit for excessive condensation or heat.

A less expensive method uses heat and moisture exchangers (HME) that act as an “artificial nose.” These devices trap exhaled water particles and heat as condensation during exhalation, helping to conserve airway moisture. Specialized filters also trap exhaled bacteria and viruses. The effectiveness of these devices depends on gas flow rates and the patient's temperature. They should be changed every 24 to 72 hours or if they become saturated with secretions, because this creates resistance to gas flow. HMEs are not recommended in patients who are hypothermic or who have thick and copious secretions.[2]

Suctioning is another critical aspect of airway management. There are risks associated with this procedure, and proper technique must be followed. The inhaled oxygen concentration should be increased to 100% before and during suctioning. Monitoring of the patients oxygenation status with pulse oximetry throughout the procedure is recommended.

The suction catheter should be sterile, soft, and flexible, with more than one distal opening and a proximal thumbhole to control the level of suction. Sterile gloves should be worn and sterile technique observed throughout the procedure. Closed suction systems are also available and are helpful in maintaining sterility and preventing problems associated with tubing disconnection.

Suction should be applied while withdrawing the catheter from the airway for no more than 5 seconds at a time. This procedure can be repeated two or three times as long as oxygenation remains adequate and the patient does not seem distressed. If suctioning is productive, it can be performed as frequently as every 2 to 4 hours. The risks of suctioning include hypoxemia, patient discomfort, damage to the tracheal mucosa, collapse of small airways and alveoli, and contamination of the lower airways.[2,3,6]

If the secretions are too dry to suction well or adequate humidification is not being provided, small aliquots of 913
sterile saline (0.2 ml/kg) may be instilled into the airway before suctioning. This practice has been challenged 914
because of the lack of evidence of beneficial effects coupled with the risk of introducing infection.[2,6]

Ventilator circuit tubing is a potential source of nosocomial infection and should be replaced every 48 to 72 hours. Tubing should be sterile.[2]

216.4 ANESTHESIA

There is no single ideal protocol for anesthetizing ventilator patients; the best combination for each patient will depend on the anticipated duration of ventilation, species, and concurrent diseases (Table 216-1). The anesthesia plan should be tailored to each patient, and a balanced approach should be used to minimize the adverse effects of individual drugs.

Patients should be preoxygenated before induction, and induction should provide rapid control of the airway. Potential induction agents include propofol plus or minus diazepam, ketamine and diazepam, etomidate, or thiopental. Mask inductions with inhalants should be avoided.[3,5]

Short-term ventilation (1 to 24 hours) can be accomplished with combinations of diazepam, opioids, and propofol. If a patient is ventilated for a longer period, a constant rate infusion (CRI) of pentobarbital usually in conjunction with a benzodiazepine CRI frequently is used instead of propofol.[3,5] Pentobarbital is associated with very slow recoveries, so infusions should be decreased or stopped 12 to 24 hours before weaning. Pentobarbital infusions of 3 to 4 days duration can be associated with very rough recoveries, and patients may benefit from a change to a propofol CRI for the final day of anesthesia to provide a smoother and more predictable recovery. Pentobarbital infusions of a week or longer can be associated with seizures during the recovery period; phenobarbital should be started several days before recovery.[3] Neuromuscular blockers often are used for treatment of human patients receiving mechanical ventilation; however, they require specialized monitoring, and in rare cases these agents can lead to incomplete reversal and prolonged paralysis.[2,4] Regardless of the anesthesia protocol used, it is important to reassess the patient's level of sedation frequently and to adjust infusions as needed.

Table 216-1 Anesthetic Agents for Ventilator Patients

Agent	Pros	Cons	Comments
Inhalants	Effective	Needs scavenging system, associated operator health risks Cardiovascular depression	Impairs hypoxic vasoconstriction
Propofol	Rapid onset and recovery	Expensive Causes lipemia, hypotension, respiratory depression	Not recommended for >1 to 2 days because of lipemia Can cause Heinz body anemia in cats
Etomidate	Cardiovascular sparing	Propylene glycol carrier causes hemolysis Expensive Adrenocortical suppression	CRI not recommended because of propylene glycol and high osmolality
Opioids	Cardiovascular sparing Analgesic	Panting may worsen patient-ventilator asynchrony Ileus Hyperthermia	Intermittent doses or low-dose CRI may be a helpful adjunct in addition to other agents
Pentobarbital	Effective, easy to manage as CRI Good choice for intracranial disease	Prolonged recovery Can cause seizures on recovery after use for >7 days	CRI must be decreased or stopped 12 to 24 hours before weaning
Diazepam	Good as an adjunct	Phlebitis concerns necessitate central catheter	—
Neuromuscular blockade	Reduces patient–ventilator asynchrony	Risk of incomplete reversal of paralysis Patient cannot signal if problem Muscle atrophy	Requires careful monitoring Should be used only by experienced ICU clinicians

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CRI, Constant rate infusion; *ICU,* intensive care unit.

216.5

MONITORING

Like any patient under anesthesia, ventilator patients need intensive monitoring. Basics monitoring should include continuous electrocardiography (ECG), pulse oximetry, capnography, and serial blood pressure measurements. Ideally an arterial catheter should be inserted for direct blood pressure measurements and frequent (q4h) arterial blood gas analysis. Arterial catheters usually are placed in the dorsopedal artery, which can be difficult in cats and small dogs. Cats also have less collateral circulation and may tolerate an arterial catheter for only 6 to 8 hours.[3] If arterial lines cannot be placed or maintained, then pulse oximetry, jugular venous blood gasses, and lactate levels can be used to assess oxygenation indirectly.[3,7] Thoracic radiographs are often helpful in the assessment of patients with deteriorating oxygenation, or when aspiration or pneumothorax is suspected.

Ventilator settings, including inhaled oxygen concentration, pressure and volume settings, respiratory rate, and breath patterns (mode), should be recorded regularly to monitor trends.

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216.6 FLUID THERAPY

Fluid therapy is essential to optimize perfusion and hydration of the airways while preventing pulmonary or peripheral edema. The fluid plan needs to be specific for each patient's medical issues and status. In general, animals with exudative processes (e.g., pneumonia) should be kept well hydrated, and a more conservative approach is appropriate for patients with transudative diseases (e.g., congestive heart failure, pulmonary edema).[3] Frequent physical examinations and serial monitoring of serum electrolytes, lactate, and albumin, urine output, and specific gravity can all be helpful in adjusting fluid plans. Ventilator patients have a tendency toward peripheral edema and sodium and water retention; fluid intake and output should be monitored closely. Measurement of central venous pressure and colloid osmotic pressure may be also useful in designing a fluid plan.

Intravenous catheters should be unwrapped and evaluated for phlebitis or swelling every 24 to 48 hours.

216.7 NUTRITION

Enteral nutritional support is challenging in ventilator patients because of the risks of regurgitation and aspiration and the high incidence of ileus. Inadequate nutrition is associated with worsening of respiratory muscle atrophy and increased incidence of gastrointestinal bacterial translocation. Excessive feeding can lead to hypercapnia and can exacerbate hypotension because of redistribution of blood to the splanchnic circulation. Specialized enteral formulas have been designed to reduce carbon dioxide production.[2]

Histamine-2 blocker use in ventilated humans has been associated with an increased risk of bacterial pneumonia, because gastric colonization with bacteria occurs at a less acidic pH. Sucralfate has been advocated as an alternative for gastric protection.[2]

Enteral nutrition can be provided via a nasogastric tube, gastrotomy tube, or jejunostomy tube. Postpyloric feeding may be correlated with a decreased risk of aspiration. Gastric residuals should be monitored, although the amount of residual is not well correlated with risk of aspiration.[2] Promotility agents such as metoclopramide, ranitidine, and cisapride should be considered in patients receiving enteral feedings.[8] Parenteral nutrition should be considered in patients that will not tolerate enteral feeding.

216.8 RECUMBENT CARE AND TEMPERATURE SUPPORT

Prolonged recumbency can lead to muscle atrophy, pressure sores, peripheral edema, and nerve damage. Patients should be repositioned every 4 hours and should receive passive range-of-motion exercises. Ventilator patients should be kept on sufficient padding that is changed immediately if soiled.

Frequent changes in body position also help prevent pooling of secretions in one airway region and reduce atelectasis of the dependent lung lobes. Oxygenation should be monitored carefully after changes in position. Turning may be associated with desaturation in animals with substantial pulmonary pathology; some patients will not tolerate lateral recumbency, in which case they may have to be maintained in sternal recumbency with only their hips turned regularly.[9] These patients require careful padding and attention to positioning to prevent decubitus ulcers.

Hypothermia is a common problem, because thermoregulation is depressed under anesthesia and large amounts of heat may be lost from the airway if heated humidification is not used. Patient temperature should be monitored closely with continuous temperature probes or with frequent intermittent measurements. Circulating water blankets, forced-air warming blankets, and adequate padding may help maintain a normal body temperature. Hot water bottles should be avoided or used with caution because of the risks for thermal injury.

Hyperthermia can also be a problem in the ventilated patient. Increased work of breathing from fighting the ventilator as a result of patient-ventilator asynchrony is a common cause. Excessive active warming, overheating of the breathing circuit, drug therapy, and primary disease processes are other possible contributors. The increased respiratory rate and effort that occurs in response to hyperthermia can be a significant cause of patient-ventilator asynchrony and may result in hypoxemia and patient deterioration. Active cooling measures may be necessary in addition to treating primary causes of hyperthermia.[10]

216.9 EYE CARE

Ventilator patients require eye care to prevent corneal drying and ulceration. Artificial tear ointment should be applied at least every 2 hours. If an ulcer is suspected, fluorescein staining should be performed and an antibiotic ophthalmic ointment regimen should be started (see Chapter 172, Ocular Disease in the Intensive Care Unit).

216.10 ORAL CARE

Ventilator patients will inevitably develop oropharyngeal ulceration and frequently develop lingual swelling unless meticulous oral care is performed (and possibly despite meticulous care) (Color Plate 216-1). Bacterial colonization of the oropharynx is believed to be the major cause of ventilator-associated pneumonia in human patients. Oropharyngeal bacteria can colonize the respiratory tract by migration or by microaspiration of oropharyngeal secretions. In addition, oropharyngeal ulceration can be a source of systemic bacteremia. Strict adherence to oral care protocols is beneficial in both human and veterinary patients.[11,12]

Oral care includes preventing mechanical trauma and frequent rinsing with dilute antibacterial solutions. Any sites of consistent pressure should be relieved regularly; for example, the pulse oximeter probe should be repositioned at least every 2 hours, the tongue should be protected against damage from the teeth and the ET tube with an atraumatic mouth gag. The tongue can be wrapped with gauze soaked with water or glycerin to reduce lingual drying and swelling. The mouth should be cleaned and suctioned every 4 hours and rinsed with an antibacterial mouthwash solution such as dilute chlorhexidine.[12]

216.11 URINARY AND FECAL CARE

Quantification of urine output and prevention of urine scald can be accomplished by using diapers (which can be weighed) or by inserting a urinary catheter with a sterile collection system. If diapers are used, the bladder should be palpated and expressed every 4 hours. Urinary catheters require aseptic placement and regular cleaning to reduce the risk of ascending infection (see Chapter 138, Urinary Catheterization). The colon should be palpated regularly and enemas should be used if necessary.

216.12 SUGGESTED FURTHER READING*

MC Clare, K Hopper: Mechanical ventilation: ventilator settings, patient management, and nursing care. *Comp Cont Educ Pract Vet.* **27**, 2005, 256, *A general review of veterinary patient ventilator management.*

SC Haskins, LG King: Positive pressure ventilation. In LG King (Ed.): *Textbook of respiratory disease in dogs and cats*. 2004, Saunders, St Louis, *A comprehensive chapter on ventilation in dogs and cats providing a general overview of patient care*.

JC Hendricks: Airway hygiene. In LG King (Ed.): *Textbook of respiratory disease in dogs and cats*. 2004, Saunders, St Louis, *A chapter that discusses general principles of airway management and humidification techniques*.

MS Mellema, SC Haskins: Weaning from mechanical ventilation. *Clin Tech Small Anim Pract*. **15**, 2000, 157, *A paper that provides a good discussion about weaning techniques and ventilator complications*.

* See the CD-ROM for a complete list of references

217 Chapter 217 Discontinuing Mechanical Ventilation

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217.1 KEY POINTS

- A patient must attain certain physiologic goals to be weaned from mechanical ventilation.
- Weaning can be achieved by a gradual reduction in the level of ventilator support or by using a specific weaning method.
- There are three main weaning methods: spontaneous breathing trials, pressure support ventilation, and synchronized intermittent mandatory ventilation.
- Close monitoring is necessary after disconnecting a patient from mechanical ventilation. Weaning failures require immediate action to maximize future success.

217.2 INTRODUCTION

Mechanical ventilation is not benign and the aim is to discontinue it as soon as possible. The process of discontinuing ventilator support is called *weaning* and has been the focus of a great deal of study in human medicine, although little information is available in the veterinary literature. In many patients receiving short-term ventilator support that have rapidly resolving disease processes, discontinuation is simply a matter of disconnecting the patient from the ventilator. Patients receiving mechanical ventilation for longer periods and those with complex disease processes may require a true weaning process.

A patient must attain certain physiologic goals to be weaned from the ventilator. These include adequate gas exchange without the support of aggressive ventilator settings, an appropriate ventilatory drive, and recovery from significant systemic disease such as cardiovascular instability or organ failure. However, attaining these goals does not guarantee that the patient can be weaned successfully. Prolonged mechanical ventilation (longer than 48 hours) can cause inspiratory muscle weakness that is proportional to the duration of ventilation.[1] In addition, short-term controlled mechanical ventilation can cause decreased diaphragmatic force-generating capacity, also known as *ventilator-induced diaphragmatic dysfunction*. [2] As a result, sudden discontinuation of mechanical ventilation may be poorly tolerated despite adequate gas exchange.

The weaning process must force the patient to assume some of the work of breathing to recondition the inspiratory muscles. Patients must be monitored closely subsequent to discontinuation of ventilation in case respiratory muscle fatigue develops.

Weaning from mechanical ventilation in human medicine is largely protocol driven; the weaning process is started only after specific criteria of readiness are fulfilled, respiratory performance is tested regularly in an effort to predict the likelihood of successful weaning, and management of the ventilator settings during weaning follows preset guidelines.

In veterinary medicine discontinuation of mechanical ventilation is a trial and error process that depends largely on clinician preference. It may be a gradual reduction in the magnitude of ventilator settings as the patient improves, until the clinician judges that the patient should be disconnected from the machine, or it may be a change in ventilator mode to one that requires a greater work of breathing by the patient.

217.2.1

Box 217-1 Criteria for Readiness to Wean

- Improvement in the primary disease process
- PaO_2:FiO_2 ratio >150-200 with FiO_2 <0.5
- PEEP ≤5 cm H_2O
- Normal respiratory drive
- Hemodynamically stable
- Absence of major organ failure

FiO_2, Fraction of inspired oxygen (0-1.0); *PaO_2,* partial pressure of arterial oxygen (mm Hg); *PEEP,* positive end-expiratory pressure.

217.3

WHEN TO WEAN

Although weaning criteria are poorly defined in veterinary medicine, there is generally a time when the decision is made to significantly reduce the amount of ventilatory support provided. The patient must have obtained certain physiologic goals before this step is taken (Box 217-1). The original disease process necessitating mechanical ventilation should be stable or improving. The patient needs a normal respiratory drive and should no longer be dependent on significant ventilator support for adequate gas exchange. Adequate oxygenation, as evidenced by a PaO_2:FiO_2 ratio of at least 150 to 200, is recommended before initiating weaning. A requirement for high inspired oxygen levels (>50%), high peak inspired airway pressures (>25 cm H_2O), and high positive end-expiratory pressure levels (>5 cm H_2O) to maintain oxygenation should preclude any weaning attempts. Weaning is not advised in animals that are hemodynamically unstable or have severe systemic disease such as organ dysfunction. The final stage of weaning includes disconnection from the ventilator and extubation.

217.4

ANESTHETIC CONSIDERATIONS

As soon as the patient fulfills the weaning criteria, rapid extubation is desirable. Long-acting anesthetic agents such as pentobarbital are associated with prolonged recoveries (several hours to days). Discontinuing these agents 24 hours or more before weaning is predicted to occur is recommended to prevent unnecessary prolongation of the anesthetic period. Changing to constant rate infusions of a short-acting anesthetic agent, such as propofol or a benzodiazepine, or both, for the last 1 to 2 days of the ventilation period can provide effective control of anesthetic depth and may smooth out the rough recovery associated with pentobarbital.

217.5

WEANING PREDICTION

In human medicine many indexes have been evaluated as potential predictors of weaning success. The rapid shallow breathing index (f/V_T) is the only one shown to have some correlation with successful weaning in adults. It is calculated as the ratio of respiratory rate (f) and tidal volume (V_T). Those patients who develop increased rapid shallow breathing during a spontaneous breathing trial (SBT) (marked by a higher f/V_T ratio) are more likely to fail the weaning trial. A ratio of less than 100 is used in human medicine to identify patients that can be weaned.[3] Unfortunately, even this ratio has not been a consistently reliable predictor of weaning outcome.[4] In veterinary medicine this ratio may be difficult to adapt to our patients given the variability in normal respiratory rates, but it does suggest that a fast, shallow breathing pattern during an SBT may be a poor prognostic indicator.

Measures of physiologic dead space (V_D/V_T) may be of some use in predicting successful weaning. Pediatric patients with a lower V_D/V_T measurement (≤ 0.5) were more likely to be extubated successfully than patients with higher V_D/V_T measurements (>0.65).[5] In veterinary medicine, no predictive indexes of weaning have been used or evaluated. Readiness to wean remains a clinical judgment.

217.6 WEANING A PATIENT FROM MECHANICAL VENTILATION

The process of weaning involves a reduction in the work of breathing performed by the machine with a proportional increase in the work performed by the patient. In veterinary medicine, this sometimes is achieved with assist-control ventilation modes (such as volume assist control or pressure assist control) in which the magnitude of the ventilator settings is decreased. However, this approach is not recommended, because every breath is generated by the machine; the patient is able only to increase the respiratory rate. This does not increase the patient's work of breathing adequately and if the magnitude of the ventilator settings are lowered excessively, there is a risk of hypoventilation. The three main weaning techniques are SBT, pressure support ventilation (PSV), and synchronized intermittent mandatory ventilation (SIMV).[6]

217.6.1 Spontaneous Breathing Trials

An SBT involves removing all ventilator support and monitoring the patient's ability to breathe spontaneously. This can be achieved by disconnecting the animal from the machine and allowing it to breathe an enriched oxygen source (usually with an FiO_2 similar to or above the level the patient was receiving while ventilated) via a breathing circuit (such as a Bain circuit). An alternative approach is to leave the patient connected to the ventilator and switch to a low level (2 to 5 cm H_2O) of continuous positive airway pressure (CPAP). The advantage of using CPAP is that all monitoring and ventilator alarms can remain attached and if the patient fails the SBT, ventilatory support can be reestablished rapidly. The endotracheal tube and ventilator breathing circuit increase the work of spontaneous breathing compared with the extubated state; a low level of CPAP may compensate for this effect and prevent unnecessary weaning failures.[7]

The concept behind SBTs is to use it almost as a training exercise for the patient as soon as it is considered sufficiently stable; there may be no expectation that the patient will be weaned with the initial trial. In human medicine it is commonly recommended to perform a 30- to 120-minute SBT daily from the time the patient attains adequate physiologic goals. SBTs may be a superior method of weaning from mechanical ventilation compared with PSV or SIMV in human medicine.[8] In veterinary medicine, it is more common to place patients on an SBT when they are considered ready to be removed completely from ventilator support. Evidence from the human literatures suggests that daily SBT to improve respiratory muscle strength as a prelude to successful weaning could be of benefit to many long-term ventilated small animal patients.

917
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217.6.2 Pressure Support Ventilation

PSV is a pressure-limited spontaneous breathing mode; the breath is triggered and terminated by the patient. As such, it can be used only in patients with a normal respiratory drive. The inspiration is augmented by additional inspiratory pressure as preset by the operator, but the patient controls the respiratory rate, inspiratory flow, and tidal volume of each breath. The level of pressure support can be decreased gradually as the patient improves. When the patient is stable on a low level of pressure support (i.e., <5 cm H_2O), discontinuation of ventilation can be considered. This discontinuation essentially involves an SBT. If the patient fails the SBT, it is returned to PSV at the previous or higher settings as required.

217.6.3 Synchronized Intermittent Mandatory Ventilation

SIMV is another approach to reducing ventilator support gradually. During SIMV there are both mandatory and spontaneous breaths. The mandatory breaths are synchronized with the patient's inspiratory efforts and the tidal volume of the mandatory breaths is generated totally by the ventilator (controlled ventilation). Between mandatory breaths the patient can breathe spontaneously. Weaning generally is achieved by a gradual reduction in the mandatory breath rate, which demands a progressive increase in the respiratory work performed by the patient. When the patient can maintain adequate oxygenation and ventilation with minimal machine support, an SBT is performed.

If the patient fails the SBT, SIMV is resumed. Patients may require a higher level of machine support than they did previously to recover from the effects of the SBT. When first introduced, SIMV was thought to reduce patient-ventilator asynchrony, reduce respiratory muscle fatigue, and expedite weaning. There is evidence that SIMV may worsen respiratory muscle fatigue. Two well-conducted human trials found SIMV to be the least effective method of ventilator weaning.[8,9] Because no such trial has been performed in veterinary medicine, the role of SIMV for weaning small animal patients is unknown.

217.7 MONITORING

Because it is impossible to predict how successful a given weaning attempt will be, it is vital that patients are monitored closely to rapidly identify weaning failure and reinstate ventilatory support. Monitoring requires that a dedicated caregiver observe the patient for tachypnea, anxiety, or abnormal respiratory efforts such as paradoxical abdominal-thoracic movements and nasal flaring. In addition, oxygenation status is monitored ideally by continuous pulse oximetry or intermittent arterial blood gas measurements. Ventilatory status can be determined with arterial or venous blood gas measurements and continuous capnometry. A continuous electrocardiogram, for heart rate evaluation, and arterial blood pressure measurement are also recommended. Temperature monitoring is important because hyperthermia can occur as a consequence of increased respiratory effort and will tend to further exacerbate any respiratory difficulties. Conducting weaning attempts with the patient still connected to the ventilator using CPAP will allow monitoring of respiratory parameters such as minute volume and airway pressure.

217.7.1 Box 217-2 Criteria for Failure of a Spontaneous Breathing Trial

- Tachypnea (RR >50)
- PaO_2 <60 mm Hg or SpO_2 <90%

- $PaCO_2$ >55 mm Hg or $PvCO_2$ >60 mm Hg or $ETCO_2$ >50 mm Hg
- Tachycardia
- Hypertension
- Anxiety

$ETCO_2$, End tidal carbon dioxide; *PaO_2,* partial pressure of arterial oxygen; *$PaCO_2$,* partial pressure of arterial carbon dioxide; *$PvCO_2$,* partial pressure of venous carbon dioxide; *RR,* respiratory rate; *SpO_2,* oxygen saturation.

217.8 FAILURE TO WEAN

Failure of a weaning attempt is identified by deterioration in certain physiologic parameters (Box 217-2). Significant hypoxemia or hypercapnia is an obvious indication for reinstatement of ventilatory support. Tachycardia, hypertension, and tachypnea are all ominous signs and suggest that the patient cannot be weaned during that attempt. Significant anxiety or abnormal respiratory efforts are also indications to restore ventilatory support. One author stresses the importance of preventing patient exhaustion during weaning trials because respiratory muscle fatigue is believed to delay successful weaning.[10]

Most commonly, unsuccessful weaning is a result of the incomplete resolution of the underlying disease process, although a ventilator-associated complication or new disease process can develop.

217.9 EXTUBATION

Extubation is performed subsequent to a successful SBT once adequate recovery from anesthesia has occurred. In patients ventilated via a temporary tracheostomy tube, it may be prudent to leave the tube in place for 24 hours or more in case the patient relapses and requires reinstitution of ventilatory support.

217.10 PROGNOSIS

Prognosis for successful weaning from mechanical ventilation depends largely on the primary disease process. Human and veterinary clinical studies have repeatedly reported lower weaning rates for patients requiring ventilation for pulmonary parenchymal disease (inability to oxygenate) compared with patients with neuromuscular disease processes (inability to ventilate). One retrospective study of 34 dogs and 7 cats with heterogeneous lung disease reported an overall survival to hospital discharge rate of 20% compared with 57% for animals with neuromuscular disease.[11] In a retrospective study of 148 dogs and cats receiving long-term mechanical ventilation (>24 hours), 36% of cases with lung disease were weaned and 22% survived to hospital discharge. In comparison, 50% of the animals with hypoventilation were weaned and 39% survived to hospital discharge.[12] These statistics are similar to those reported in human medicine. A retrospective study of human intensive care patients treated longer than 24 hours with PPV reported a survival to discharge (from the intensive care unit) rate of 29.3% in the group with oxygenation impairment and 57.8% in the group with ventilatory insufficiency.[13]

217.11 SUGGESTED FURTHER READING*

L Brochard, A Rauss, S Benito, et al.: Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med*. **150**, 1994, 896, *A comparison between SBTs, PSV, and synchronized mandatory ventilation as weaning methods, PSV being most effective*.

A Esteban, F Frutos, MJ Tobin, et al.: A comparison of four methods of weaning patients from mechanical ventilation. *New Engl J Med*. **332**, 1995, 345, *An excellent study evaluating the relative effectiveness of four weaning techniques: intermittent mandatory ventilation, PSV, multiple daily SBTs, and once daily SBTs; significantly shorter periods to extubation associated with once daily or multiple daily SBTs than the other methods*.

DR Hess, RM Kacmarek: In *Essentials of mechanical ventilation*. ed 2, 2002, McGraw-Hill, New York, *An easy-to-read, excellent basic reference for all aspects of mechanical ventilation. Although a human text, a lot of the information is applicable to veterinary medicine*.

K Hopper, SC Haskins, PH Kass, et al.: Indications, management, and outcome of long-term positive-pressure ventilation in dogs and cats: 148 cases (1990-2001). *J Am Vet Med Assoc*. **230**, 2007, 64, *The largest veterinary study of mechanical ventilation. Includes only patients receiving ventilation for 24 hours or longer and reviews many aspects of the management and associated complications in these animals*.

* See the CD-ROM for a complete list of references

Appendix

Appendix 1 Calculations and Constant Rate Infusions

Parameter	Formula	Normal Values*
Cardiovascular Parameters		
Arterial oxygen content	CaO_2 (ml/dl) = (Hb (g/dl) × 1.34 × SaO_2) + (PaO_2 (mmHg) × 0.003)	19-21 ml/dl
Cardiac index	CI (ml/kg/min) = CO (ml/min) ÷ BW (kg)	120-200 ml/kg/min
	CI (L/m^2/min) = CO (L/min) ÷ Body surface area (m^2)	3.5-5.5 L/min/m^2
Oxygen delivery	DO_2 (ml/kg/min) = CI (ml/kg/min) × CaO_2	20-35 ml/kg/min
Oxygen consumption (Fick Equation)	VO_2 (ml/kg/min) = CI (ml/kg/min) × (CaO_2 – CvO_2)	4-11 ml/kg/min
Oxygen extraction ratio	OER (%) = (CaO_2 – CvO_2) ÷ CaO_2	20%-30%
Systemic vascular resistance	SVR (mmHg/ml/kg/min) = (MAP – CVP) ÷ CI (ml/kg/min)	0.5-0.8 mmHg/ml/kg/min
	SVR (dynes.sec.cm^{-5}) = (MAP – CVP) × 79.9 ÷ CI (L/min/m^2)	1600-2500 dynes.sec.cm^{-5}
Pulmonary vascular resistance	PVR (mmHg/ml/kg/min) = (PAP – PAOP) ÷ CI (ml/kg/min)	0.04-0.06 mm Hg/ml/kg/min
	PVR (dynes.sec.cm^{-5}) = (PAP – PAOP) × 79.9 ÷ CI (L/min/m^2)	125-250 dynes.sec.cm^{-5}
Stroke volume	SV (ml/beat/kg) = CI(ml/kg/min) ÷ HR	1.5-2.5 ml/beat/kg
	SV (ml/beat/m^2) = CI (ml/min/m^2) ÷ HR	40-60 ml/beat/m^2

Mean arterial blood pressure	MAP (mmHg) = ([Systolic BP – Diastolic BP] ÷ 3) + Diastolic BP	Dogs = 80-120 mmHg
		Cats = 100-150 mmHg

Oxygen-Related Parameters		
Alveolar air equation	P_AO_2 (mmHg) = FiO_2 (P_B – P_{H2O}) – ($PaCO_2$ ÷ RQ)	Depends on FiO_2 and barometric pressure FiO_2 = 0-1 P_{H2O} = 47 mmHg RQ = 0.8-1
A-a gradient	A-a (mmHg) = P_AO_2 – PaO_2	Depends on FiO_2
PaO_2/FiO_2 ratio	P/F = PaO_2 (mmHg) ÷ FiO_2 (0–1)	500
Shunt equation	Qs/Qt (%) = (CcO_2 – CaO_2) ÷ (CcO_2 – CvO_2)	<5%
Fluids and Acid–Base		

Daily maintenance fluid rate	Dogs = BW(kg)$^{0.75}$ × 132 (ml/day) Cats = BW(kg)$^{0.75}$ × 70 (ml/day)
	44-66 ml/kg/day
Calculated osmolarity	Calculated osmolarity (mOsm/L) = 2(Na + K) + (BUN (mg/dl) ÷ 2.8) + (Glucose (mg/dl) ÷ 18)
Osmolar gap	Osmolar gap (mOsm/L) = measured osmolality – calculated osmolarity
Anion gap	AG (mEq/L) = (Na + K) – (HCO$_3$ + Cl)
Total body water	TBW (ml) = 0.6 × BW (grams)
Free water deficit	Free water deficit (ml) = TBW × ([Na measured ÷ Na normal] – 1)
Nutrition	
Resting energy requirement	RER (kcal/day) = BW(kg)$^{0.75}$ × 70
	RER (kcal/day) = BW (kg) × 30 + 70 (patients 2 – 30 kg)

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* Normal values can vary depending on several factors including the laboratory performing the measurements, the method used to obtain the measurements, and the species. Normal values listed here are for dogs (unless noted otherwise) and may differ for feline patients.*A-a*, Alveolar-arterial gradient; *AG*, anion gap; *BP*, blood pressure; *BUN*, blood urea nitrogen; *BW*, body weight; CaO_2, arterial oxygen content; CcO_2, end capillary (pulmonary) oxygen content; *CI*, cardiac index; *CO*, cardiac output; CvO_2, mixed venous oxygen content; *CVP*, central venous pressure; DO_2, oxygen delivery; FiO_2, fraction of inspired oxygen; *Hb*, hemoglobin; HCO_3, bicarbonate; *HR*, heart rate; *K*, potassium; *MAP*, mean arterial blood pressure; *Na*, sodium; O_2, oxygen; *OER*, oxygen extraction ratio; $PaCO_2$, partial pressure of arterial carbon dioxide; P_AO_2, partial pressure of alveolar oxygen; PaO_2, partial pressure of arterial oxygen; *PAOP*, pulmonary artery occlusion pressure; *PAP*, pulmonary artery pressure; P_B, barometric pressure; *P/F*, $\mathrm{PaO_2}/FiO_2$ ratio; P_{H2O}, water vapor pressure; *PVR*, pulmonary vascular resistance; *Qs/Qt*, percent of arteriovenous shunt; *RER*, resting energy requirement; *RQ*, respiratory quotient; SaO_2, arterial oxygen saturation; *SV*, stroke volume; *SVR*, systemic vascular resistance; *TBW*, total body water; VO_2, oxygen consumption.

Appendix 2 Expected Compensatory Changes to Primary Acid Base Disorders in Dogs

Primary Disorder	Expected Compensation
Metabolic acidosis	↓ $PaCO_2$ of 0.7 mmHg per 1 mEq/L ↓ HCO_3
Metabolic alkalosis	↑ $PaCO_2$ of 0.7 mmHg per 1 mEq/L ↑ HCO_3
Respiratory acidosis: acute	↑ HCO_3 of 0.15 mEq/L per 1 mm Hg ↑ $PaCO_2$
Respiratory acidosis: chronic	↑ HCO_3 of 0.35 mEq/L per 1 mm Hg ↑ $PaCO_2$
Respiratory alkalosis: acute	↓ HCO_3 of 0.25 mEq/L per 1 mm Hg ↓ $PaCO_2$
Respiratory alkalosis: chronic	↓ HCO_3 of 0.55 mEq/L per 1 mm Hg ↓ $PaCO_2$

From de Morais HAS, DiBartola SP: Ventilatory and metabolic compensation in dogs with acid-base disturbances, *J Vet Emerg Crit Care* 1:39, 1991.

HCO_3, Bicarbonate; *$PaCO_2$*, partial pressure of arterial carbon dioxide.

Appendix 3 Constant Rate Infusion Calculations

Micrograms Per Kilogram per Minute

$$\text{Drug dosage rate}\,(\mu\text{g}/\text{kg}/\text{min}) \times \text{Body weight}\,(\text{kg}) \times \text{Volume of fluid}\,(\text{ml})$$

$$\text{Delivery rate}\,(\text{ml}/\text{min}) \times 1000$$

$$= \text{Number of mg to add to the volume of fluids}$$

Milligrams per Kilogram Per Hour

$$\text{Drug dosage rate}\,(\text{mg}/\text{kg}/\text{hr}) \times \text{Body weight}\,(\text{kg}) \times 25(\text{hr})$$

$$\text{Concentration of drug}\,(\text{mg}/\text{ml})$$

$$= \text{Volume of drug (ml) to add to a 250 - ml bag of fluids and run at } 10\ \text{ml}/\text{hr}$$

Appendix 4 Common Drug Dosages for Constant Rate Infusions

Drug	Comment	CRI Dosage
Atracurium besylate	Loading dose: 0.2-0.3 mg/kg IV Will require PPV	4-9 μg/kg/min
Butorphanol	Loading dose: 0.2-0.4 mg/kg IV	0.1-0.4 mg/kg/hr
Calcium gluconate	Continuous ECG monitoring required	10 mg/kg/hr
Diazepam	Administer via central vein Will adsorb to plastic	0.2-1.0 mg/kg/hr
Diltiazem	Loading dose: 0.15-0.25 mg/kg slow IV	5-20 μg/kg/min
Dobutamine	Monitor ECG	Dogs: 2-20 μg/kg/min Cats: 1-5 μg/kg/min
Dopamine	Extravasation may cause necrosis	Low: 1-4 μg/kg/min Mid: 5-10 μg/kg/min High: 10-20 μg/kg/min
Epinephrine	Potent α-agonist and β-agonist	0.005-1 μg/kg/min
Esmolol	Loading dose: 0.05-0.1 mg/kg IV Can cause hypotension	50-200 μg/kg/min
Fentanyl	Loading dose: 1-5 μg/kg IV May require PPV with higher dosages	Analgesia: 0.05-0.3 μg/kg/min Anesthesia: Dogs: 20-100 μg/kg/hr Cats: 10-50 μg/kg/hr
Furosemide	Loading dose: 0.5-1 mg/kg IV	0.5-1 mg/kg/hr
Hydrocortisone	Loading dose 1 mg/kg IV	Dogs: 0.6 mg/kg/hr
Hydromorphone	Loading dose: 0.05 mg/kg IV	0.01-0.05 mg/kg/hr
Regular insulin	Monitor blood glucose Will adsorb to plastic, so flush 50 ml of infusion solution through infusion line initially	Dogs: 2.2 U/kg/day Cats: 1.1-2.2 U/kg/day
Isoproterenol	May cause hypotension	0.04-0.08 μg/kg/min
Ketamine	Loading dose: 1 mg/kg IV	0.1-1 mg/kg/hr
Lidocaine	Loading dose: Dog: 2-4 mg/kg slow IV Cat: 0.25-0.75 mg/kg slow IV Use with caution in cats	Dog: 25-80 μg/kg/min Cat: 10-40 μg/kg/min
Mannitol	Loading dose: 0.5 g/kg over 20-30 minutes	1-2 mg/kg/min
Medetomidine	Loading dose: 1 μg/kg IV	Analgesia: 1-3 μg/kg/hr
Metoclopramide	—	Dogs: 0.01-0.02 mg/kg/hr Cats: 0.05 mg/kg/hr
Midazolam	—	0.1-0.5 mg/kg/hr
Milrinone	Loading dose: 30-300 μg/kg	1-10 μg/kg/min

Morphine sulfate	Loading dose: 0.2 mg/kg IM May require PPV at higher dosages	Dogs: 0.1-1 mg/kg/hr Cats: 0.1-0.3 mg/kg/hr
Nicardipine	—	0.5-5 μg/kg/min
Nitroprusside	Requires constant blood pressure monitoring	0.5-10 μg/kg/min
Norepinephrine	Primarily α-agonist	0.05-2 μg/kg/min
Pentobarbital	May require PPV	0.2-5 mg/kg/hr
Phentolamine	Loading dose: 0.05-0.1 μg/kg	5-30 μg/kg/min
Phenylephrine	Pure α-agonist	1-3 μg/kg/min
Phosphate	Requires serum phosphate and calcium monitoring	0.01-0.06 mmol/kg/hr
Procainamide	6-8 mg/kg IV over 5 min Dogs only	10-40 μg/kg/min
Propofol	2-6 mg/kg IV	0.05-0.4 mg/kg/min
Pyridostigmine	—	0.01-0.03 mg/kg/hr
Sufentanil	Loading dose: 1-2 μg/kg	0.1 μg/kg/min
Vasopressin	Off-label use for vasoplegia	1-4 mU/kg/min
Verapamil	0.05-0.15 mg/kg IV	2–10 μg/kg/min

CRI, Constant rate infusion; *ECG*, electrocardiogram; *IM*, intramuscular; *IV*, intravenous; *PPV*, positive-pressure ventilation.